Endocrinology

THE GLANDS AND THEIR FUNCTIONS

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To

W. B. C.

Expounder and Exponent of Wisdom

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PREFACE

This book represents an attempt to present a succinct account of the more significant aspects of endocrinology as known today. The field is large and is extending rapidly in many directions. It has engaged the interests of investigators and writers in all of the biological and most of the social sciences. A mere catalog of the significant contributions to the literature runs to hundreds of pages.

To select the most meaningful from this rich store of material is not easy. The choice is necessarily somewhat arbitrary. Strive as one may for objectivity, in the very process of selection the subjective element bulks large. The problem presents a twofold danger. In the attempt to bring out the human meanings of the data one can easily descend to marvelmongering. On the other hand, concern with sobriety of statement may lead to failure to do justice to the really remarkable advancement in knowledge that has been made in the past half century. It is impossible in a book of this scope to include all of the significant evidence, either recent or older.

At every step in the writing I have striven for accuracy of statement and for fairness in emphasis. While trying to avoid the intrinsic mendacity of oversimplification, I have likewise sought to prevent the facts, by their complexity, from obscuring their own meaning.

In this undertaking I have drawn frequently upon material utilized in a former work, *The Tides of Life*, which appeared in 1933. The material has been brought up to date and amplified with an eye particularly to the needs of biologists, psy-

chologists, premedical students, and those physicians who desire a not too technical introduction to the science of the hormones I have also tried, however, to keep for the most part within the comprehension of the intelligent general reader

Many of the facts of endocrinology are of significance in numerous settings I have not hesitated, therefore, to repeat statements from one section to another when I conceived this to be to the advantage of the reader I have perhaps departed somewhat from the conventional pattern in books of this sort by giving the choice to data from human cases rather than to the results of animal experimentation when they would serve the exposition approximately as well

In assembling the data, I have drawn freely upon the writings of fellow students in the field Only a part of the obligations thus incurred are indicated in the text and in the literature lists To these various authors and to others not explicitly mentioned a sense of gratitude is truly felt

At the end of individual chapters have been cited a few writings selected to afford the reader further access to the field In general, the choice has fallen upon monographic reviews, books, and individual articles that afford good literature lists In a final chapter mention is made of various sources of information dealing with the field of endocrinology in its wider aspects

The Memorial Foundation for Neuro Endocrine Research
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I. HORMONES—THE CHEMICAL REGULATORS

THE SCIENCE of *Endocrinology* stems from the primitive belief in organ magic—the belief that man can augment his powers by consuming appropriate portions of his fellow man or of animals taken in the chase In the older days the warrior thought to increase his courage by eating the heart of his enemy Today the retarded child improves his intellect by eating the thyroid of a sheep

As early as the beginning of the Christian Era such practices had come under the sanction of orthodox medicine Diseases of one sort or another were believed to be due to the lack of mysterious substances derived from the different individual organs It followed that the diseases were to be cured by supplying the lacking substances artificially As a system of procedure this method of treatment came ultimately to be known as *opotherapy* Among the early proponents of the system were Celsus and Dioscorides Liver of the wolf was prescribed for diseases of that organ, brain of the hare for nervousness, or lung of the fox for respiratory disorders From time immemorial, sex gland material has been employed to increase erotic prowess As Paracelsus phrased the doctrine, "heart cures heart, spleen spleen, lungs lungs"

It is historically interesting that modern interest in the *hormones* was largely stimulated by an attempt to revive the ancient practice of opotherapy Brown Sequard, a famous French savant, found himself in his later years overtaken by general debility With the courage, perhaps, of desperation he

began to treat himself by injections of testicular extracts The experiments were reported before the *Societe de Biologie* of Paris on June 1, 1889—a date that is sometimes cited as "the birthday of endocrinology" So eminent was the scientist and so spectacular the beneficial results he claimed to have experienced that world wide interest was immediately aroused The very meager stream of contributions that up to this time had been devoted to the science of endocrinology soon was swollen to a flood

Whether Brown Sequard's results were more than a triumph of suggestive therapy is doubtful But growing out of his error, if error it was, has come a development in the field of medicine more significant perhaps than any other since the discovery of the bacterial origin of disease The evidence is now conclusive that what we are—physically, mentally, sexually, and emotionally—depends in no small measure upon the functions of our endocrine glands They co-operate in an important way in the regulation of our activities in health and modify the course, when they do not primarily determine, our diseases A fundamental new principle has been added to physiology

Several of the endocrine organs had been recognized anatomically by Galen as early as the second century, but nothing was understood as to their functions until comparatively recent times Many fanciful speculations were offered, and some ideas that were not too wide of the mark were hit upon, but simple observations had to be supplemented by special and laboriously evolved technics before the functions could precisely be determined

Brown-Sequard's pursuit of waning vigor may have been directly inspired by the words of Thomas Willis, who wrote, some three hundred years ago "The blood pours out something—through the spermatic arteries to the genitals, so also it receives as a recompense a certain ferment from these parts—to wit certain particles imbued with a seminal tincture are carried back to the blood which make it vigorous and inspire into it a new and lively virtue" A century later the great

Albrecht Haller expressed a belief that some intrinsic fluid is elaborated also by the thyroid, spleen, and thymus and poured into the blood system At about this same time, what amounts substantially to the modern view of the significance of the internal secretions was more elaborately formulated by Theophile de Bordeu, a fashionable physician at the Court of Louis XV "It was his ambition," says Garrison, "to confirm and uphold the humeral pathology of Hippocrates and he regarded the three Hippocratic stages of disease—irritation, coction, and crisis—as dependent upon the glandular and other secretions Bordeu's slender reputation today is concentered in a single idea—the doctrine that not only each gland, but each organ of the body, is the workshop of a specific substance or secretion which passes into the blood and that upon these secretions the physiological integration of the body as a whole depends"

Important as are the hormones, they are not the sole or even the chief agents by which such integration is achieved Many of our adaptive reactions are brought about directly by the nervous system which receives stimuli from the surrounding environment or from within the body itself and distributes impulses in appropriate fashion to bring about suitable reactions to either outer or inner circumstances The nerve impulses are especially useful in evoking rapid adjustments to episodic events There are other activities of the organism, however, that correspond to general policies in an industrial concern and that can be carried out without frequent individual orders These represent such functions as growth, development, and, to a less extent, the digestive and reproductive activities It is in these latter functions that the endocrine glands play especially important regulatory roles The internal secretions are largely used, too, in the slower adaptation to environmental events such as changes of temperature, of nutrition, or of the physiological status of the body—as in pregnancy

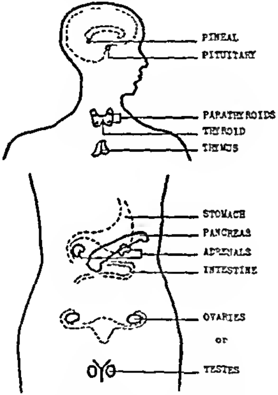
The *internal secretions*, or hormones, are derived, as are secretions generally, from structures known as glands These

are, in effect, chemical laboratories which take up from the blood a variety of materials and elaborate them into new substances having special properties In case of the ordinary glands, such as those which secrete tears or saliva, the products are transferred through ducts to their appropriate spheres of action The internal secretions, however, are discharged into the blood stream to be distributed throughout the body In the older view these substances were thought of only as stimulating agents, hence were designated as *hormones* (from the Greek *hormao*, "I excite") But the term is to some extent a misnomer in that the influence may be repressive rather than excitatory Sharpey Schafer coined the term *chalone* to designate the inhibitory substances but this, too, is somewhat inept in that a given internal secretion may be excitatory or inhibitory depending upon the tissue affected or the conditions under which it operates

The organs now known to produce hormones are the *pituitary* or *hypophysis*, the *thyroid*, the *parathyroids*, the *adrenals*, the *pancreas*, the *stomach* and *intestines*, the *ovaries*, and the *testes* Other organs to which endocrine functions are more or less plausibly ascribed are the *pineal*, the *thymus*, the *liver*, and the *spleen* The locations of the chief endocrine organs are shown in the accompanying transparent silhouette figure

Before anything was clearly understood as to the particular functions of the various glands, physicians had come to recognize several diseases that are now known to be due to disorders in their functions As early as 1786, an English practitioner, Caleb Parry, had noted the occasional simultaneous occurrence of a group of symptoms of the disease now known as *exophthalmic goiter* These were protrusion of the eyeballs, palpitation of the heart, and swelling of the thyroid gland Eight cases of the disorder were collected by Parry and published after his death in 1825 The disease was further studied by Italian, German, and English physicians between 1802 and 1840, hence, in modern medical literature, the disorder is

known in their respective countries as *Flajani's*, *Basedow's*, or *Graves' disease*. That excessive thyroid secretion might be the cause of exophthalmic goiter was suggested by Rehm in 1884. The suggestion was supported by the experience of a patient



Transparent silhouette of human body showing the locations of the endocrine organs

of Notthaft who took a thousand thyroid tablets within a five weeks' period and developed the major symptoms of that disorder In 1850, Curling, another Englishman, observed that defective thyroid development was accompanied by "sym-

metrical swellings of fat tissue at the sides of the neck, connected with defective brain development" The disease that he had seen is the now well known malady, *myxedema*

In 1840, the German Mohr had his attention drawn to "a remarkable and fatal obesity" in the elderly wife of a gardener She showed beginning imbecility, loss of memory, general somnolence, and partial blindness Post mortem examination disclosed a tumorlike degeneration of the pituitary body This case was the first recognized example of the modern *pituitary obesity* It is an interesting coincidence that Mohr's case was reported in the same volume in which Basedow described exophthalmic goiter The relation of the pituitary gland to body size began to be suspected a century and a half ago through the observations of its abnormality in giants, but it remained for the Frenchman Pierre Marie, in 1886, to convert the suspicion to plausible theory, by describing accurately a case of *acromegaly* and stressing the accompanying overgrowth of the pituitary gland

The first clinical inkling of the function of the adrenal glands was afforded in 1849 by a British clinician, Addison, who described a disease that still bears his name In a classic monograph published six years later he clearly described the symptoms of *Addison's disease* He emphasized the bodily weakness, low blood pressure, discoloration of the skin, and digestive disorders that are still regarded as the cardinal symptoms He recognized that the cause of the disease is destruction of the adrenal glands

Apparently the first morphological evidence that materials can actually pass from glands into the circulation was offered by King in 1836 Under the microscope he saw indication of the transfer of colloid from the thyroid gland into the lymphatics and thence into the general circulation About the same time Gulliver also described microscopic spheroids in the adrenals and in the blood coming from them Usually, however, formal credit for first demonstrating the process of internal secretion is given to Claude Bernard, who in 1848 re

ported the discovery that sugar stored in the liver in the form of *glycogen* is discharged as dextrose directly into the blood rather than through the ducts of the organ after the fashion of an ordinary secreting gland The term "internal secretion" is no longer applied to substances like sugar, but is restricted to those having a more specific regulatory function

There is good reason to believe that chemical control is a primitive method by which the various parts of the body are brought to develop and work in harmony The method is found in the lowest forms of animals, those completely devoid of a nervous system But, as Sharpey-Schafer has pointed out, such animals are also devoid of a circulatory system, hence distant organ control was not thereby provided The fundamental functions such as digestion or growth even in the higher animals are primarily under hormone control Reproduction, with its numerous bodily and psychic adaptations, is likewise strikingly dependent upon hormone factors That we are dealing in case of the hormones with primitive mechanisms is suggested, too, by the fact that these substances are completely interchangeable from one species to another It makes no material difference whether insulin for the treatment of diabetes in man be obtained from another man, an ox, or a fish These facts suggest that chemical control and, in the higher animals, specific hormone control, have come up from a remote ancestral period Nervous control as we know it in man and his nearer relatives is of much later origin

The *internal secretions*, proper, are, many of them, fairly simple chemical substances, but some are proteins and are correspondingly complex Several have been obtained as pure crystalline bodies Considered as drugs some are remarkably potent Adrenalin, for example, when introduced directly into the blood stream exercises a recognizable effect in concentration as low as one part in four hundred millions This dilution can be visualized as that which would be produced by the addition of one ounce of a given substance to the contents of ten thousand water tanks, each holding six hundred and

twenty five gallons Dosages of some of the more effective hormones recently isolated are expressed in "gammas," one gamma being equal to one sixty five thousandth of a grain Thyroxine, the hormone of the thyroid gland, is so potent that one grain in actual tissue use causes the chemical processes of an adult human being to proceed a third faster than they would in its absence It is estimated that the total amount of thyroxine circulating in the body at any one time is only about one fourth of a grain Three and a half grains suffice for an entire year But this small pinch of thyroid hormone makes the difference between sluggish imbecility and normal health

Though secreted in almost infinitesimal amounts, the hormones wield a mighty influence A baby born without thyroid tissue is a misshapen, drooling object with protruding tongue and abdomen who never, of his own resources, becomes more than a stunted, bandy legged imbecile Lack of another hormone from the pituitary gland prevents growth so that the individual remains a diminutive dwarf An oversupply of the same hormone in childhood leads to gigantism If the over growth begins after puberty, when well rounded development is no longer possible, excessive tissue formation takes place in such parts of the body as are still able to respond, the result being a gross, misshapen individual who seems to have reverted to a gorilla type An excess of one of the adrenal hormones causes a marked accentuation of the masculine sex traits In the male this results in an exaggeration of virility In the female it produces a masculinized caricature, the deep voiced, coarse-featured, bearded lady of the circus side show In different varieties of dogs similar bodily deviations have become hereditary The Pekingese is a dwarf, the Great Dane a giant, and the bulldog an acromegalic Keith and Stockard, among others, have discussed at length the possibility that the evolution both of animal types and of human beings may have depended upon antecedent changes in the endocrine glands Conclusive evidence on the point, however, is lacking

The practical application of endocrinology in the treatment

of diseases lags far behind the available anatomical and physiological knowledge. The lag is due in large measure to the difficulty of transferring results obtained in experimental animals directly to human beings The therapeutic use of thyroid, insulin, adrenalin, and certain pituitary extracts has often been conspicuously successful. On the other hand, the administration of parathyroid extract, extract of adrenal cortex and various hormones related to the reproductive functions, has often been disappointing Other preparations that have shown potency in laboratory experimentation have as yet had only limited use in human disorders.

In addition to the curative agents that have resulted from endocrine research, the science has also contributed significantly to human welfare by affording new insights into a variety of disease processes Some of these are adiposity, excessive hair growth, abnormal pigmentation, abnormal blood pressure, menstrual disorders, and disturbances in sugar metabolism

One of the fascinating new chapters in the book of science is the story of the internal secretions Their potency is almost unbelievable. Their influence is pervasive in all that we do and are. In the present they co-operate in determining the forms of our bodies and the working of our minds In the past they may have set the pattern of our advancement through the ages. We shall now turn to the story in greater detail.

II. THE ADRENAL GLANDS

DURING THE centuries of the Dark Ages medicine ventured to add little to the records of the old Greek authorities Although the adrenal glands must have been seen innumerable times by huntsmen, warriors, and butchers, they had escaped the scholarly notice of the elder anatomists and thus remained unknown to science until the medieval darkness was dissipated by the revival of learning They were described by Eustachius in 1563, but with the recognition of their existence, and such description as naked-eye observation permitted, progress again ceased Many a slow step in the development of biologic methodology had to be taken before the first inkling of their functions was gained The experimental method to which medicine chiefly owes its modern progress was introduced by John Hunter only in the late seventeenth century Prior to that time clinical experience seldom brought forth anything more substantial than uncritical lore Physiology up to that time consisted largely, as it had for centuries, of more or less plausible speculations Some of these are well illustrated in the story of the adrenal itself

In 1716, the Academy of Sciences of Bordeaux sponsored a series of competitive essays on "What is the Use of the Adrenal Glands?" To Montesquieu was assigned the task of appraising the contributions He reported

> Some have imagined that these glands are placed in the situation where they occur in order to hold up the stomach which would otherwise press too hard on the veins of the kidneys Others have imagined them to strengthen and consolidate the venus plexus

which is in contact with them—conclusions which appear to have escaped the ancients who were content with simply expressing ignorance of the functions of these glands Bartholin was the first to relieve them of the stigma of performing so menial an office He is of opinion that a humor which he terms "black bile" is preserved within their cavity and believes that there exists a communication between the capsules and the kidneys, this humor serving to dilute the urine

Some anatomists teach that the only use of the glands is to collect the humidities which leak out of the great vessels surrounding them, others have held that a bilious juice is formed within them and, being carried to the heart, mingles with acidity which is there present and excites fermentation, this being the cause of the heart's movements. Others consider that the humor within the glands is nothing more than a lacteal juice which is distributed by the mesenteric glands.

We have one author who affirms the existence of two kinds of bile, one, grosser, secreted by the liver, the other, more subtile, secreted by the kidneys with the aid of a ferment This ferment flows from the glands through ducts, the existence of which is completely unknown to us—and of which we are threatened with perpetual ignorance

Finally, stating that none of the memoirs submitted could be looked upon as satisfying the legitimate curiosity of the Academy, the critic concludes "Chance perhaps may some day effect what all these labors have been unable to perform" Nearly a century and a half was to elapse before that chance was realized

EARLY INVESTIGATIONS

For the first clue to the functions of the adrenal glands we are indebted to the acumen of a British physician, Thomas Addison In the year 1855, he published a monograph reporting eleven cases of the disease that still bears his name His description of the disorder is a medical classic

The leading and characteristic features of the morbid states to which I would direct attention are anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of colour of the skin occurring in connection with a diseased condition of the suprarenal capsules

This singular dingy or dark coloration usually increases with the advance of the disease, the anaemia, languor, failure of appetite and feebleness of the heart become aggravated, a darkish streak usually appears on the commissure of the lips, the body wastes the pulse becomes smaller and weaker, and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires

Addison was able to show that the destruction of the adrenals, to which the symptom complex is due, is commonly caused by local tuberculosis Other destructive processes, however, such as cancer of the gland or simple atrophy, may lead to the same end result

Addison's monograph at once aroused the interest of the physiologists of his day Brown Sequard almost immediately began a series of experiments in which he removed the adrenals from dogs, cats, rabbits, and guinea pigs The results were always the same—marked prostration, followed by early death The adrenal problem seemed fairly on the way to solution Then occurred a remarkable example of the halting of scientific progress by a valid discovery Two other investigators repeated Brown-Sequard's experiments but unfortunately, as we see now, selected white rats as subjects The animals survived in good health, hence it appeared that adrenal deficiency, as such, was a harmless condition, the fatal results in Brown Sequard's animals were ascribed to the formidable surgical procedures that were involved It was not until years later that the survival of the rats was explained this animal is commonly provided with enough accessory adrenal tissue to be able to dispense with the glands proper Most other animals, however, are not so equipped Following the unfortunate dis-

covery of the rat's immunity to adrenal extirpation, research again languished until, for a second time, the world was indebted to a British clinician for the resumption of progress

Dr George Oliver had been empirically using a variety of glandular preparations in the treatment of his patients Particularly, he had been struck with some of the effects on circulation. In 1893, he and Schafer decided to undertake a collaborative investigation of the physiological effects of some of the gland extracts which he had been using clinically Unique among these, adrenal material was found to be characterized by a highly interesting property, namely, "an extraordinary effect upon the tone of the heart and arteries, transcending that of any known drug" The experiments were reported before the British Physiological Society in March, 1894 At the same time, however, two Polish investigators, Cybulski and Szymonowicz, had independently hit upon the same observation and reported it a year later

This new knowledge cast the whole picture in different perspective Brown Sequard's work now seemed credible despite the anomalous results in rats The new knowledge could be formulated in a consistent fashion It appeared that removal of the adrenals resulted, as a general rule, in extreme lethargy and circulatory failure Conversely, adrenal extract had a remarkably stimulating effect upon the circulatory apparatus It appeared then that the glands have as their function the formation of a hormone that serves to keep the circulatory organs working at an efficient level This theory soon took precedence over the alternate belief that had gradually come into vogue, namely, that the glands are significant primarily as agents for the destruction of hypothetical "toxins" that are formed in the body in the course of the normal physiological processes

Adrenal extracts at once became the objects of research in various countries with the aim of isolating the hypothetical hormone to which the invigorating effect upon the circulation is due The major step in the isolation was taken by Abel, who

obtained the active fraction as a simple addition product which he named *epinephrine* From this product there was soon obtained the hormone itself in pure crystalline form This relatively simple chemical feat was performed by Aldrich and by Takamine independently and almost simultaneously

An American pharmaceutical firm by which these investigators were employed began promptly to market the material under the name *Adrenalin*—which is merely a Latin transliteration of the Greek term, *epinephrine* Despite this commercial use of the name, adrenalin has largely come into use the world over in preference to Abel's term, epinephrine, though the latter is still in use by some punctilious American writers The contraction *adrenin*, too, has had considerable vogue and is perhaps the most suitable generic term for the adrenal medullary hormone

Following the work of Abel the next major step in the history of adrenal physiology was taken by Elliott (1905) From a variety of experiments he came to the important generalization that extracts of adrenal medulla have precisely the same effects throughout the body as does stimulation of the sympathetic nervous system—the sweat glands, however, forming an exception to the general rule The sympathetic system has important regulatory influences upon many involuntary activities When aroused to activity it causes the pupils to dilate, the skin to become pale, and the hairs to rise The activities of the digestive tract promptly cease and its blood supply is mostly shunted to other structures A similar reaction occurs in the circulation of various of the other internal organs Thus many of the sluices are cut off and, the heart beating more forcefully as an additional factor, the blood pressure is markedly increased The blood vessels in the skeletal muscles are an exception to the general rule, they open wider instead of contracting and thus, in a measure, let off some of the high pressure The airways into the lungs enlarge Even the composition of the blood is changed by increased discharge of sugar (dextrose) from the liver Following the publications

of Elliott nearly a decade was to elapse before the rationale of this seemingly random melange of effects was to be offered by Cannon in his "emergency theory"

Investigators in the earlier period were overimpressed with the complementary facts that destruction of the adrenals results in circulatory weakness and that administration of adrenal extracts increases circulatory vigor The assumption that the adrenals contribute a continuous supply of a stimulating hormone seemed to afford a sufficient *raison d'être* for their existence Thus the *tonus theory* of adrenal function was born

While this theory is mostly of historical interest, further attempts to confirm or disapprove it led to the discovery of several additional significant facts The first serious doubt was cast upon the tonus theory when it appeared that disconnecting the adrenals from the circulation was followed by no significant disturbance in blood pressure, for at least a matter of hours, whereas the known effects of injected adrenin are all over within a few minutes If the function of the adrenals were to keep the circulatory system under constant tonic stimulation, results of sudden enforced abstinence should appear at once The possibility remained, however, that adrenin might have a more slowly acting function to the same general end it might play a necessary role in keeping up the nutrition of the circulatory structures or of preserving their responsiveness to sympathetic impulses On that hypothesis time might be required for the development of tissue weakness In such a case injections of adrenin into an animal showing the effects of adrenal deficiency should improve its condition Experiments to test this possibility showed that the slow injection of adrenin over a considerable time to imitate its constant secretion in a normal animal quite failed to relieve the symptoms of the deficiency, and indeed served to hasten death Not only did the sympathetic nerve fibers fail to have their reactivity restored, but their responses to stimulation were even often impeded Another discovery was that if the assumed adrenin tipple of the normal animal were cautiously exaggerated by

the injection of more of that hormone, the blood pressure—which served as an indicator of sympathetic activity—instead of increasing, as theory demanded, was often lowered. Finally, it was discovered that the administration of adrenin in quantities barely adequate to elevate the blood pressure brought the activities of the digestive system to a standstill It seemed obvious that a mechanism that could maintain blood pressure only at the expense of stopping digestion could not be of general utility.

THE EMERGENCY THEORY

Such was the status of the problem when Cannon entered the field in 1912 He had just completed a series of classic researches on the motor activities of the alimentary canal He had had many occasions to observe the movements of the digestive organs as disclosed by the newly discovered X rays He had been struck by the fact that if the animal under test fell in good naturedly with the laboratory procedures the digestive activities ran smoothly on But if the subject rebelled the experiments were frequently halted by a stubborn quiescence of the alimentary canal The initial stopping of the activities might have been due merely to arousal of the sympathetic system by the anger of the animal, but the ire soon passed, whereas the digestive tract might remain inactive for an hour or more To explain the persistence of the quiescence Cannon postulated that it might be due to prolonged secretion of adrenin, setting up a sort of chemical reverberation of the initial sympathetic reaction The known fact that sympathetic stimulation causes adrenal discharge rendered the hypothesis attractive

Put to experimental test, the new idea received immediate support Procedures were evolved for obtaining blood from the vena cava in the adrenal region without causing pain to the animal When such blood was drawn without exciting the subject, and applied to sensitive test tissues, no evidence of the presence of adrenin could be detected But if the blood was

collected while the subject was excited by the presence of a barking dog, it was found to have acquired a new property quite like that of the hormone

It appeared, then, that under conditions of strong excitement (fear or anger) the adrenal glands discharged at an augmented rate The remarkably variegated effects of injecting adrenin were already known, but their meaning was puzzling Cannon's "emergency theory" was formulated as an explanation It was postulated that under conditions of quiet existence adrenin secretion is in abeyance But in time of special stress, under the influence of pain or of its emotional equivalent, fear or anger, adrenin is discharged and serves to adapt the animal to the demands of the stressful occasion Commonly, such occasions call for vigorous action Large muscle masses come into use and demand mobilization of the supporting physiological resources The heart begins to pump more forcefully, sending more fuel material and oxygen to the muscles and carrying away the augmented wastes The fuel as it is used up is replenished from the glycogen stores of the liver The air passages dilate to permit freer breathing Constriction of the blood vessels of the skin and of the abdominal organs increases the blood supply available to the muscles and to the directing nervous system The digestive functions go into temporary quiescence In short, the whole animal is reintegrated—internally patterned—for muscular activity The various effects described are precisely those that result from injections of adrenin Thus the effects of strong emotion on bodily functions seemed to be clarified

But the new theory at once encountered difficulties of two sorts It was widely and promptly misunderstood and misquoted Emotions were at last reduced to chemistry! This gratuitous extension of the theory ignored the fact that an animal can react strongly to emotions in complete absence of the adrenals—until the ultimate metabolic effects preclude the possibility of reacting to anything As a matter of fact, Cannon's theory was merely that discharged adrenin serves to re

inforce the activities of the sympathetic system, activities that can go on in an effective way without any such reinforcement

The more serious difficulty encountered by the theory, however, was the failure of certain investigators to confirm the experimental evidence in its favor This led to a prolonged controversy which in turn led to several refinements of technic and the accumulation of much supplementary evidence The negative evidence finally boiled down largely to the fact that the adrenals of a grossly traumatized animal in the depths of anesthesia do not significantly respond to increased stimulation In confirmation of the theory, it appeared that if a muscle is stimulated to the point of fatigue the administration of adrenin immediately increases its capacity for work Furthermore, adrenin causes the blood to coagulate more rapidly —an effect of obvious utility should the stressful occasion leading to adrenin discharge result in bodily injury To the same adaptive end, a reserve supply of blood from the spleen is at once thrown into the circulation to compensate for that lost while coagulation is getting under way

Various other supporting facts may be found in the technical literature There is now no reasonable doubt that under conditions of special stress adrenin is automatically discharged into the circulation and serves to reinforce the activity of the sympathetic nervous system whereby the body is adjusted for vigorous activity But whether any adrenin at all is secreted under ordinary circumstances is still a matter of dispute That it is of only episodic importance is suggested by the work of Harris and Ingle (1940), who showed that the ability of rats to undergo prolonged muscular work was not lowered by destruction of the adrenal medulla

The "emergency function" of the adrenals affords a physiological basis for the old aphorism, "worry is worse than work" When, as the result of a stressful condition, the sympathetic adrenal mechanism is thrown into activity the body is at once integrated for muscular endeavor The high blood pressure and the quiescence of various abdominal organs are of obvious

advantage. But when, on the other hand, circumstances do not permit the biologically normal muscular activity, such as fighting or running away, these changes serve merely to disrupt the adjustments for repose. Furthermore, the emotional tension, failing of release by appropriate overt activity, persists and prolongs the maladjustments. The interference with the normal equilibrium thus set up may lead to chronic high blood pressure, gastric ulcer, and a variety of other functional and metabolic disorders—including many of those which go to make up the picture of "neurasthenia." A discussion of the intimate part played by the hypothalamic region of the central nervous system in those various adjustments and maladjustments would go beyond the scope of this work. The matter is further discussed by Alvarez.

ANATOMY OF THE ADRENALS

In the higher vertebrates the adrenal glands are paired organs, those in man weighing, together, about ten grams (a five-cent piece weighs five grams). In the primates one adrenal perches like a cocked hat over the upper pole of each kidney to which it is closely adapted. Because of this location the structures are often called the *suprarenal* glands, but in animals other than primates—which continue the ancestral habit of running on all fours—the term *adrenal* is more accurately descriptive in that the glands lie ahead of, rather than above, the kidneys as the prefix "supra" indicates. Adrenals proper are not found in animals below the vertebrate level of existence, though a few invertebrates have glands which yield extracts somewhat resembling those of the adrenal medulla. But beginning with the lowest fishes and extending up to man, adrenals are found in all known animals—a fact which at once suggests their fundamental importance.

In man and the higher vertebrates generally the adrenal, *in cross section*, is seen to consist of two parts: a soft, brownish red central portion, the *medulla*, and a surrounding outer por-

tion, the *cortex* The medulla is composed of an irregular net work of strands, among which capillaries and expansions of these, the *sinuses*, occur profusely The individual cells of the medulla vary in form but are mostly elongated and arranged perpendicularly to the sinus walls This arrangement no doubt facilitates rapid discharge of their secretions into the blood stream—a function which demonstrably can take place within a few seconds Even during the earlier embryonic period the medullary cells show a marked affinity for salts of the metal, chromium It is from this characteristic that the term *chromaffin tissue*, which is applied both to the medulla and to various bits of similar outlying tissue, is derived

The *cortex* is usually described as composed of three zones Immediately beneath the capsule of the gland lies the external or *glomerular layer* Next is the intermediate zone, the *fasciculata*, which is composed of short columns of cells This zone blends without sharp demarcation into the inner zone, the *reticularis* This latter, as its name implies, forms a network which is more or less interpenetrated with medullary cells and is characterized by relative profusion of sinuses

In some rodents the inmost cortical zone is more sharply differentiated than in most animals to form the so-called *x zone* This is fairly prominent in young females and disappears only gradually in adulthood, but in males its development is halted at an early stage It appears that the x zone has a specific function of forming sex stimulating secretions In animals other than rodents this function seems to be carried out by cells scattered throughout the cortex Both the x zone tissue and these interpolated cells can be more or less successfully differentiated by a special staining method, utilizing the dye, fuchsin The cells are, therefore, sometimes designated as constituting the *fuchsinophile* tissue

By the application of osmic acid it can be seen that the cells of the cortex, generally, are largely made up of fatlike substances (*lipins*) These comprise true fats, lecithin and choles

terol—substances which are also predominant chemical components of the brain This similarity in composition offers a hint in explanation of the fact that in the rare clinical condition of *anencephaly*, in which an infant is born without a higher brain, the adrenal cortex is also lacking or is very small Both abnormalities may be due to a fundamental defect in lipid metabolism The amount and distribution of the cortical lipins vary greatly in different animals They may, in part at least, represent secretory products, though it is doubtful that the adrenal glands have the predominant role in fat metabolism which is often ascribed to them There is evidence that the cholesterol of the cells increases during rest and diminishes during activity In various diseases all the lipins become depleted During pregnancy the cortex enlarges and cholesterol is a conspicuous component of the increased substances

The vital importance of the adrenals is suggested by their remarkably rich *blood supply*—the richest of any organ of the body Six times their own weight of blood passes through the glands each minute

The main *suprarenal artery* comes off directly from the aorta, enters the hilum of the gland and supplies mainly the medulla, accessory vessels are received from the phrenic and adrenal arteries These latter principally supply the cortex, through a finely distributed network of smaller vessels A somewhat similar arrangement is seen in the venous supply, which consists principally of a large central vein and superficial plexuses A peculiarity of the adrenal veins is the inclusion in their walls of longitudinal muscle bundles, the contraction of which can close off the smaller vessels, thus permitting local regulation of the circulation

It is only in the higher forms that the cortex and the medulla of the gland are combined to form a composite organ In most animals the cortical tissue exists as paired, independent structures, the so-called *interrenal bodies*, whereas the medulla is represented by the *chromophile bodies*

The two parts of the composite adrenals, or their homologues the interrenal and chromaffin bodies, are of different *embryological origin* The cortex is derived from a portion of the early mesoderm in the anterior part of the forming body cavity The future cortical cells appear first as the *interrenal buds*, these are gradually detached from the lining membrane and coalesce into larger structures The first trace of the differentiated interrenal tissue in man is found when the embryo is about a fourth of an inch long at the twenty fifth day of development By the time the length of the embryo has doubled, the adult structure of the gland is fairly clearly established

The medulla arises from small groups of cells which first appear in the abdominal plexus when the embryo is about twenty milli meters long These cells, the *pheochromoblasts*, closely resemble other groups of cells in the same vicinity, the *sympathoblasts*, from which the sympathetic nervous system arises Both kinds of cells begin early to invade the primitive interrenal structure, the sym pathoblasts taking the lead The pheochromoblasts take a position in the central part of the organ, pushing the interrenal cells more and more to the periphery By the end of the fourth month of foetal existence they have become transformed to the adult type of medullary cells and the penetration has ceased The emigration of the sympathetic cells, however, continues until after the time of birth

Not all of either type of cells become incorporated into the finished adrenal gland Various groups of the pheochrome ele ments become associated with the ganglia of the sympathetic nervous system to form the *paraganglia* Some of the inter renal buds go to form *accessory cortical bodies* which may be found in the adult in the tissues around the adrenal glands proper, in the broad ligaments of the ovaries, along the spermatic veins, and imbedded in the kidneys, liver, or other abdominal organs

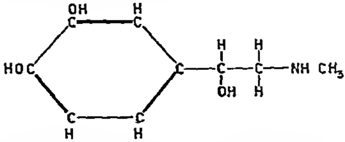
That the adrenals have some important function in the prenatal stage of existence is suggested by their relatively early

development During the third month of foetal life they are the most conspicuous structures inside the body cavity At birth they are still relatively large but in early infancy they undergo a rather rapid involution, much of the cortical tissue being broken down and absorbed At this time of involution the glands are notably vulnerable and may become invaded by fatal hemorrhages

The *innervation* of the adrenals follows the pattern of the visceral organs, generally, the glands receiving both sympathetic and parasympathetic nerve fibers Those distributed to the cortex make connection only with the blood vessels (Fulton), hence any influence which they may have on the secretory processes is by virtue of their action on the local circulation The innervation of the medulla is unique in that this structure amounts, itself, to a modified sympathetic ganglion Its controlling fibers are therefore of the preganglionic order

THE MEDULLARY HORMONE—ADRENIN

Chemically, adrenin is a relatively simple substance despite its formidable technical name, "dihydroxy methylaminoethylol benzene" or "dihydroxyphenyl hydroxyethyl methylamine" Its elementary composition is denoted by the formula $C_9H_{13}O_3N$ Its molecular structure is



Its composition was confirmed by Stolz who succeeded in reproducing it synthetically Natural adrenin, like various other

hormones, has the property of turning the plane of polarized light to the left, i e, it is *levorotatory* The synthetic product, however, is optically inactive, since it consists not only of levorotatory but also of a compensatory amount of physiologically inactive *dextrorotatory* (right twisting) adrenin

Despite the fact that it can be produced synthetically, adrenin is obtained mostly from the adrenal glands of animals Commercially, it is essentially a by product in the manufacture of cortical derivatives It can be extracted from the gland substance with water or with weak acids and precipitated from the solution by concentrated ammonia In the purified state it forms needle shaped crystals It is slightly soluble in alcohol but not in the ordinary lipoid solvents

It is a reducing agent and yields characteristic color reactions green with iron salts and red with iodine, ferricyanide, or gold chloride It readily combines with the oxygen of the air to form a pink, then brown, and finally blackish substance—the "black bile" of Bartholin The natural precursor of adrenin in the body is not precisely known, though it is believed to be *tyrosine* or *phenylalanine* At any rate tyrosine can be oxidized to a compound closely related to adrenin and this can be transformed into a black pigment resembling the natural *melanin* that is found in the skin It is this chemical relationship that is cited to account for the dark pigmentation of the skin in Addison's disease As its name indicates, adrenin contains an *amine* group and it is to this group that the biological activity has been ascribed, whereas the color reactions seem to be due to its diphenol group

The characteristic color reactions of adrenin can be used for the identification and assay of the substance, but for many biological investigations these chemical tests are not sufficiently delicate For such purposes recourse is taken to one or other of the sensitive biological reactions In principle these are simple Any solution to be assayed for its adrenin content is applied to living tissues of one sort or another and the effects noted in comparison with those of a known quantity of the

pure substance Among the tissues that are thus used are bits of intestine, heart, or uterus kept alive in an oxygenated salt water bath or the denervated heart left within the body The circulatory system of the frog or that of the rabbit's ear can also be used For many purposes simply injecting the solution into the blood stream of one of the common laboratory animals and noting the rise in blood pressure is sufficient Some of these tests are astonishingly delicate

In the practice of medicine, adrenin is widely used as a *drug* In cases of collapse, as after electric shock or drowning, an injection of adrenin directly into the arrested heart may be lifesaving Almost as spectacular may be the relief of symptoms of allergic shock when the drug is introduced by vein, or even intramuscularly A more commonplace use is to swab adrenin on an abraded surface to stop oozing hemorrhage It can be employed as a spray to shrink the mucous membranes of the nose When given with local anesthetics, it blanches the tissues and thus prolongs the action by holding the injection impounded It can be given by intratracheal spray or by intramuscular injection for the relief of the bronchiolar spasms of asthma Occasionally it may be of use for the quick elevation of blood pressure or of blood sugar, but these effects are so short lasting as usually to be of little importance These various effects of adrenin are paralleled by those of the drug *ephedrin,* which has the practical advantage of having more prolonged action

TISSUE HORMONES—SYMPATHIN

In addition to adrenin, the body produces another similar (sympathomimetic) substance *sympathin* It is found in sympathetic nerve trunks and is apparently liberated whenever the sympathetic fibers distributed to any tissue are aroused Perhaps the easiest way to demonstrate its production is by stimulating the cut nerves going to the tail of a cat The first effect is a fluffing of the hairs to form a "bottle brush " Shortly afterward the blood pressure rises and other evidences of sympa

thetic activity are seen In most respects the physiological effects of sympathin are like those of adrenin, but certain differences indicate that the two substances are not identical

As has long been known, adrenin has a stimulating effect on some tissues and a depressing effect on others Whether sympathin shared in this characteristic presented an interesting problem Researches by Cannon and Rosenblueth showed that, unlike adrenin, sympathin exercises its twofold effect by virtue of intrinsic differences in the hormone itself Thus, from tissues which are stimulated by the sympathetic nervous system an excitatory hormone, *sympathin E*, is liberated In tissues that are depressed by such stimulation *sympathin I* is produced

The effects of sympathin seem, for the most part, to be exerted in the regions where it is released, but if liberated in excess it is picked up by the circulation to influence the functions of other organs which are sensitive to it

The color of many fishes and lizards is determined by special pigment cells, the *chromatophores* When expanded, these give prominence to the color and, when contracted, cause lightening of the tint The chromatophores are controlled in part by nervous impulses and in part by various hormones such as sympathin, adrenin, *intermedin* from the pituitary gland, and perhaps other *tissue hormones* not yet identified Parker has made extensive studies on the occurrence of sympathin and other tissue hormones—especially in the lower forms

The actions of sympathin suggest a physiological principle that may be applicable to nerve impulses generally The tissues may be supplied with local stores of very reactive substances which are easily liberated when the nerve impulses reach their terminal goals These substances may be held in masked form in some sort of loose chemical combination Only a minute amount of energy supplied by the nerve impulse would be needed to liberate the stimulating substance which, in turn, would be sufficiently potent to set off the reactive tissue cells much as a fulminating cap is used to set off a relatively more inert charge of dynamite

Whether all nerve impulses thus impinge upon the reacting tissues through the agency of a chemical mediator is not yet known, but that parasympathetic impulses are thus transmitted by *acetylcholine* is now well established. Furthermore, acetylcholine is known to be liberated within the sympathetic nervous system itself when impulses pass from preganglionic to postganglionic neurons. The transmission of ordinary impulses to skeletal muscle is also accompanied by liberation of this same substance. The possibility that transmission of impulses from neuron to neuron within the central nervous system may be carried out through chemical (hormonal) means remains open. Such a mechanism would afford an explanation for various phenomena difficult otherwise to understand, e. g., polarization of synaptic conduction.

THE HORMONES OF THE ADRENAL CORTEX

In its influence upon numerous bodily functions, the hormone of the adrenal medulla is useful but not critically necessary to life. It is the cortex that is indispensable. In the lower forms removal of the interrenal tissue, leaving the chromaffin bodies intact, is a fatal operation, whereas the reverse procedure, removing the chromaffin but sparing the interrenal structures, is relatively harmless. A corresponding operation in the higher forms is more difficult in that experimental destruction of the adrenal cortex necessarily interferes with the circulation and innervation of the medulla, but the problem can be successfully approached indirectly. When one entire adrenal is removed the animal is little, if any, the worse for the operation. The second adrenal may then be removed, a portion at a time, at intervals, until the minimal amount necessary to sustain life is determined. It is thus found that from one fourth to one eighth of one gland permits survival. Whether this fragment contains any medullary cells is immaterial.

The crucial importance of the cortex rather than the medulla of the gland having been discovered, investigators through

out the world made many attempts to isolate its active principle or principles While hints of its presence in gland extracts were frequently detected, satisfactory proof of the existence of a cortical hormone was so difficult to obtain that research on the subject had come to be regarded as a forlorn hope The credit for having the courage and patience finally to secure convincing evidence is shared by Hartman and by Stewart and Rogoff Their successful researches were published at about the same time, in 1927, and in more detail over the succeeding two or three years The earlier extracts were effective in prolonging the survival period of adrenalectomized animals, but only in postponing the fatal issue Within a short time, however, sufficient potency was secured to protect the animals indefinitely The credit for the latter success was shared by Swingle

The earlier investigators assumed that the vital function of the cortex centered in a single hormone and this Hartman named *cortin* It is now known, however, that adrenal extracts afford several active substances and the earlier cortin was probably a mixture of these Nevertheless, the term is still useful as referring to potent, life sustaining cortical extracts but without implying much as to individual constituents

The best yield of cortin is obtained from glands collected immediately after death and either frozen or processed at once It disappears rather rapidly from gland substance kept at body temperature At best, the yield is so small as to indicate that little of the hormone is stored in the gland the extract from a mass many times that of the animal's own adrenals is required daily to sustain life Like several other hormones, cortin is generally more efficacious when administered by vein than when taken by mouth But preparations can be made by adsorption on charcoal that have relatively high potency on oral administration, and at least one of the newer fluid products is reported to be as potent when given to rats in their drinking water as when injected hypodermatically

A given amount of hormone is considerably more efficacious when injected in divided doses than when given as a single quantity Smaller animals require relatively more of the extract than do larger ones to maintain health Hartman has found, for example, that per pound of body weight a rat needs forty times, and a cat four times, as much cortin as does a man Larger doses are required when the subject is exposed to exercise, cold, pregnancy, trauma, or infections If the extract is withheld until an animal lacking adrenals goes into collapse, more is required to revive it than would have been the total amount necessary to maintain it over the same period Similarly, the advent of a crisis in human cases demands larger doses Despite its profound effects in adrenal deficiency an excess of cortin apparently results in no harm

Active chemical study of cortical extracts dates from about 1930 The work has been carried on mainly by three groups —Reichstein and his associates at Zurich, Wintersteiner and Pfiffner at Columbia, and Kendall, Mason, and associates at the Mayo Foundation The work up to 1939 is reviewed by Mason, whose account may be consulted by those especially interested.

All three laboratories have depended upon alcohol for at least the first stage of extraction of the tissue mass After distribution of the primary extract between petroleum ether and strong alcohol, and then each again between ether and water followed by the use of Grignard's reagent for the separation of ketonic from non-ketonic material, Reichstein obtained seven or eight compounds Acetylation of the residues and adsorption analysis enabled him to raise the number to twenty-two The Mayo group were impressed, however, by the loss of potency when these more elaborate chemical methods were employed and have largely restricted their methods to distribution between water and chloroform and between water and benzene They have thus been able (1939) to isolate nine compounds and, with further application of acetylation and

adsorption to the residues, two more The previous isolation of ascorbic (C-vitamic) acid or vitamin C from cortical material by Szent Györgyi may also be mentioned

Most of the substances that have thus been obtained are without demonstrated significance in the animal economy, but six compounds have been found to have cortinlike activity These are all *steroids* and are built up around a phenanthrene cyclopentane nucleus All six together, however, fail to account for more than a minor portion of the activity in the original extract That part of the extract which produces most of the activity passes from water into benzene with relatively little loss, but it has not yet been isolated In their composition and molecular arrangement the known active compounds all closely resemble the sex hormone, progesterone, which itself, in large doses, protects an animal from adrenal deficiency The differences consist chiefly of varying distribution of oxygen within the molecule

The first active crystalline substance for which cortinlike activity was demonstrated—the "compound E" of Kendall—can be oxidized to *adrenosterone*, which has the property of producing comb growth in capons, hence is a male-sex factor It is possible to go from compound E by another chemical route to *androsterone*, an active male-sex factor which occurs in the urine of normal men

The most active crystalline compound so far discovered is *desoxycorticosterone* which is, chemically speaking, 21-hydroxy progesterone Desoxycorticosterone acetate is about three times as potent as the uncombined form The next most active derivative is the "compound B" of Kendall, which is called by Reichstein *corticosterone* Kendall's "compound A" is of about the same order of activity Corticosterone, when tested in adrenalectomized dogs, has been found to have one sixth the potency of desoxycorticosterone The Swiss group have also reported the preparation of *17-hydroxyprogesterone*, which has about the same potency as corticosterone

What other active ingredients may be found in cortical extract, and to what extent each participates in the physiology of

the cortex, remains for the future to disclose No one or no combination of the active substances now known accounts for the full potency of the gland

Some hints as to the properties to be anticipated in isolated pure fractions may be obtained from a consideration of the differential effects of various sorts of unfractionated extracts Hartman has reported the preparation of one such, the *sodium-factor*, which specifically influences the electrolyte pattern of the body He had previously reported the separation of a *lactation factor*, different from cortin, that supports milk production in adrenalectomized rats Simple glycerine extract of adrenal cortex has been shown, when given by mouth, to bring about sustained supranormal blood pressure, a property not found in ordinary cortin Also, cortin, as now known, does not account for the influences that the adrenal glands are known to exercise in the sex field

A research by Secker, reported in 1938, throws important light on the relationship of the adrenal cortex to the sympathetic nervous system In brief, it was found that when the sympathetic fibers to given organs were stimulated to the point at which they no longer transmitted impulses their functions could be promptly restored by cortical extract Thus the old "tonus theory" of adrenal function again becomes tenable, but in terms of cortin rather than of adrenin

Whether these various effects are due to single active principles or to combinations of single principles remains for future research to determine Likewise, the problem remains open to what extent the various active bodies that the chemists are isolating represent true hormones and to what extent interesting artifacts

EFFECTS OF CORTICAL DEFICIENCY

The properties of the true cortical hormone or hormones can best be deduced from a knowledge of the effects of cortical deficiency in man or in experimental animals The cardinal *symptoms* of adrenal deficiency are fatigue and lethargy to-

gether with weak heart action and low blood pressure, these are strikingly improved by cortin One of the first signs of impending disaster from adrenal deficiency is loss of appetite, which is promptly regained when the potent extract is administered In human subjects pain in the back, abdomen, and legs is frequently reported As the disorder progresses nervous and mental symptoms supervene, the first of these being insomnia, which is also the last to disappear under treatment The subject then shows irritability, irrationality, poor judgment, and un-co-operativeness As the fatal issue approaches, either man or animal is likely to go into convulsions, to be succeeded by complete collapse and coma Unless cortin is promptly administered death soon follows, all the usual restoratives being without avail If cortin is given in time the patient begins to show improvement from within one to several hours, more promptly, ordinarily, in animals than in man The symptoms disappear in reverse order to that in which they develop Having been restored through the use of cortin, the subject maintains a rather normal condition for about three days without further treatment, after which the symptoms again begin to appear Rowntree states that nothing in the whole field of medical treatment so nearly approaches the miraculous as does the effect of cortin on a patient suffering from acute adrenal failure

Animals deprived of their adrenals are defective in their ability to respond to exposure to *cold* by increased heat production This ability can be restored by the use of cortin That this represents loss of general vigor rather than any specific effect is shown by the fact that adrenal deficiency leads likewise to loss of ability to resist *heat* Patients having Addison's disease dislike hot weather and experimental animals are easily prostrated by elevated temperature To some extent, the inability to withstand cold may be ascribed to a decrease in the rate of oxygen consumption, that is, depression of the *basal metabolic rate* After removal of the glands, the rate commonly falls from 10 to 20 per cent, at which level it remains

approximately stationary until shortly before death when a further drop, associated with fall in body temperature, takes place In cases of adrenal deficiency cortin normalizes the basal rate, though it has little or no effect on this process in normal subjects

A striking manifestation of adrenal deficiency is interference with the *growth* process—a fact which is utilized in the assay of cortical extracts A closely associated phenomenon is slowness in the healing of wounds, which process involves tissue growth Cortical deficiency also lessens the ability to withstand toxic substances, either administered as such or resulting from infections

One of the most constant evidences of higher grades of adrenal deficiency is defective excretion of *nitrogenous waste products*, via the kidneys The urea content of the blood may be more than doubled Similarly, the water exchange in the body is depressed, both intake and output being reduced, but the former to the greater extent, leading to dehydration and loss of blood volume In the later stages of the deficiency the blood sugar usually falls to a notably low level as does also the amount of glycogen stored in the liver

Cortical deficiency also causes marked disturbance in the *salt metabolism* of the body As the disorder progresses the titer of potassium, magnesium, and calcium of the blood gradually increases Contrariwise, the blood sodium and blood chlorides fall while their output in the urine increases Recent work with "tagged atoms" (radioactive isotopes) shows that rats deprived of their adrenals excrete sodium salts more rapidly, and potassium salts less rapidly, than normal That these aberrations of salt metabolism are a matter of some import is shown by the fact that keeping the animals on a low potassium diet, and especially giving increased amounts of sodium chloride, permits their maintenance with materially less cortin than would otherwise be needed, and in some cases with little or no cortin at all In this connection may be cited the case of a child suffering from adrenal deficiency who had acquired a

habit of eating inordinate quantities of table salt When he was placed in a hospital for treatment he was arbitrarily deprived of this indulgence, whereupon he promptly died of adrenal deficiency

It has long been a matter of record that in adrenal deficiency the *thymus gland* and other lymphoid structures become hypertrophied, and this despite the fact that the thymus is especially susceptible to malnutrition which is itself a characteristic of adrenal failure Associated—perhaps causally—with the lymphoid hypertrophy is an increased susceptibility to anaphylactic reactions Conversely, when an animal is suddenly subjected to adverse conditions an "alarm reaction" which includes cortex hypertrophy and thymus atrophy takes place (Selye)

Finally, adrenal deficiency has important repercussions in the *sex field* In males loss of sex drive is a fairly early symptom and, as the disorder progresses, degeneration of the cells of the testes occurs In female animals estrus ceases Should the subject be pregnant, abortion occurs Mothers with newborn young when deprived of their adrenals are unable to produce milk for them

The question may now be asked which of these various manifestations represents the *critical feature* of adrenal deficiency? A failure in oxygen metabolism, which demonstrably does occur, might account for the fatigability, circulatory asthenia, susceptibility to cold, and final collapse How this factor could account for the disturbed salt metabolism, however, is not obvious and the disturbances of sugar metabolism would also be somewhat difficult to account for on this basis The disturbed salt metabolism also might account for many of the symptoms of adrenal deficiency and is believed by some investigators actually to account for all of them Swingle has emphasized disturbance of body fluid regulation as of most importance He points out the resemblance between adrenal collapse and ordinary surgical shock and ascribes both conditions to inability of the capillaries to retain water Hartman has long held that there is no one feature to which primacy

can be ascribed, but that the symptomatology of adrenal deficiency arises from generalized interference with cell metabolism Britton has believed for many years that interference with carbohydrate metabolism is the crucial phenomenon

That the cortex has an intimate relationship to sugar metabolism is evident from the recent work of Long and others If the pancreas of an animal is destroyed, it promptly goes into a condition closely similar to diabetes mellitus in man, in which state the blood sugar is much increased If, however, a condition of adrenal-cortex deficiency is added to the pancreatic deficiency, the animal loses its ability to make sugar from protein and fat and hence the diabetic manifestations are materially lessened and life is prolonged Conversely, giving cortical extract restores the ability to make and store carbohydrate, the diabetes is then aggravated and death hastened

Still another possibility of explanation is found in the work of Verzar who has maintained that the fundamental function of the cortex is to control the processes by which phosphorus enters into and determines a variety of metabolic activities

That at least two hormones are involved in these various manifestations is suggested by the fact that, of the purified products, those having most influence on the electrolyte pattern has least on the carbohydrate metabolism and vice versa.

The work of Secker, previously cited, reopens the question whether failure of sympathetic nervous function may not be a fundamental factor in the manifestations of adrenal deficiency

DISORDERS OF THE ADRENAL GLANDS

The Medulla

Diseases of the endocrine glands, in general, give rise to two sorts of clinical disorders—those due to underfunction and those due to overfunction of the glands These conditions may be due to abnormal amounts of the gland tissue or to abnormal levels of activity in glands that are normal in size

In the older and less critical clinical literature a condition known as *hypoadrenia* was widely discussed Implicit in the diagnosis was the assumption that the symptomatology was due to inadequate secretion of adrenin With the overthrow of the tonus theory of medullary function upon which it rested, the concept of hypoadrenia seemed no longer tenable and of recent years little has been heard of it On general principles it can be assumed that the adrenal medulla, just as any other organ of the body, is subject to functional weakness, but if such a condition actually does occur it would be manifested only by failure of functions normally sustained by adrenin If, as the evidence indicates, adrenin has no important function except in times of special stress, medullary deficiency should be detectable only in a lessening of the ability of the individual to muster his resources for vigorous activity It would thus merge into a condition of general "low vitality" It could presumably be diagnosed only by a therapeutic test, that is, by a favorable response to injections of adrenin Aside from asthma—in which the local drug effect is important—no such condition is known to exist Should such be discovered in the future, it will probably be found among the disorders now vaguely defined as "neurasthenia" As a practical matter, however, before hypoadrenia could be either diagnosed or treated with adrenin some method would have to be found of administering the hormone in a vehicle that would gradually and continuously liberate it in active form

That adrenin is sometimes formed and secreted in excessive amounts is well known The resulting disorder, *hyperadrenia*, is manifested clinically as *paroxysmal hypertension* The chief symptom of the disease is sudden increase of blood pressure —even up to three hundred millimeters—with normal pressure levels between attacks Increased amounts of sugar in the blood and in the urine are also sometimes noted The individual spells may last for only a short time or for several hours Accompanying symptoms are pallor, blanched or cold extremities, tremor, dyspnea, sweating, nausea and headache, accompanied

usually by anxiety and extreme nervousness The cause of the disorder is commonly a tumor made up of *pheochrome* cells This may be situated in either the adrenal medulla or in one of the paraganglia From such tumors adrenin can be extracted, sometimes in large quantity In a few instances the condition has been diagnosed before death and cured by the removal of the tumor Recovery after such removal is usually rapid and complete, but there may be a residual enlargement of the heart which only gradually recedes

Other conditions which are sometimes ascribed to excessive secretion of adrenin are so-called *sympathicotonia* and *chronic high blood pressure* For reasons set forth in the earlier discussion of the tonus theory, neither of these conditions can logically be ascribed to oversecretion of adrenin They could, however, and perhaps often actually do, arise from overactivity of the cortex Supporting the possibility is the fact that high blood pressure is often found in association with that type of cortical overactivity known as adrenal virilism Also, the fact that prolonged hypertension can be induced by giving cortical extract is apposite.

The Cortex

Adrenal cortical deficiency is clearly recognizable in two distinct forms and somewhat less clearly in a third In a previous section attention was called to the vulnerability of the adrenals during their rapid involution at the time of birth Associated with this destruction of tissue severe hemorrhage may occur, giving rise to the condition of *acute* adrenal insufficiency sometimes known as *adrenal apoplexy* In its onset the disorder resembles an attack of pneumonia with rapid breathing and fever The baby quickly becomes apathetic and cyanotic and frequently develops a petechial rash (minute hemorrhages in the skin) Vomiting and convulsions follow and death from shock is the usual outcome This may occur within a day or may be delayed for three weeks If the hemorrhage breaks through the gland capsule into the body cavity the ordinary manifesta

tions of internal bleeding are added to the symptomatology

Rapid destruction of the cortical tissue from any cause other than hemorrhage should give rise to essentially the same picture According to Goldzieher, such destruction occasionally does occur—usually as a result of severe acute infection of the glands This commonly is seen in association with infection elsewhere in the body It is most often observed during childhood, but can occur at any period of life

Much more common, or at least more commonly recognized, is *chronic* deficiency of the cortex In its severe form the resulting disorder is known as Addison's disease It is usually due to tuberculosis of the glands but it may arise from any destructive process such as syphilis, tumor, or even simple atrophy Such atrophy may be the result of a preceding inflammation or it may be due to inadequate supplies of *corticotropin* from the pituitary gland The symptoms of Addison's disease may include all of the manifestations of cortical deficiency discussed in previous paragraphs As a *diagnostic* feature, darkening of the skin is especially important, the discoloration being due to accumulation of the pigment melanin in the basal layers The lining of the mouth may also be darkened The tint ranges from yellowish brown to black, depending upon the amount of melanin that is deposited The disease is rare in children It occurs most frequently at about the age of thirty and more often in men than in women Hereditary liability does not seem to be an important factor

The *onset* of Addison's disease is usually gradual, with loss of strength and endurance commonly in the foreground of the picture The characteristic weakness of the circulation is usually detected only later Another early sign is lack of appetite and aversion to fat in the food—a feature that may be correlated with the inability of the body to convert this substance to sugar Loss of weight usually is noticeable fairly early and its appearance at any time in the course of the disease is of serious import Sensitiveness to cold and even reduction of the body temperature are characteristic In the later stages,

decline of sexual desire and power in men and depression of menstruation in women usually occur, though the latter function may persist until death The course of the disorder may be, and commonly is, interrupted from time to time by *crises*, any one of which may end fatally They may be induced by mild infections such as colds, physical exertion, emotional shock, or even dietary indiscretion The crises usually begin with acute digestive upsets

Although the *progress* of Addison's disease is usually slow, it may be rapid, ending in death within a few weeks The average period of survival when the disorder is due to tuberculosis is about thirteen years, when due to atrophy it is longer (Guttman)

The *diagnosis* of Addison's disease in its full blown form is relatively easy, but borderline and atypical forms may present difficult problems The most meaningful criteria are low blood sodium, increased blood urea and blood calcium, and marked reduction in the blood volume When adequate technical skill is available, a chloride concentration test is the most reliable diagnostic resource It amounts to giving a fixed dose of table salt under standard dietary conditions and demonstrating the occurrence of diminished sodium chloride in the blood together with high urinary output of the same salt The test, however, puts a strain on the vital resources of the patient and should not be undertaken without adequate provisions at hand for meeting a crisis, should such occur

Details of *treatment* cannot be considered in a work of this scope In general, the mainstay consists in the use of potent cortical extracts supplemented with table salt in large doses Diets low in potassium are theoretically indicated but are of somewhat doubtful practical utility Because of the reduced capacity of the liver to store carbohydrate, between meals feeding is advisable The addition of vitamin C to the diet is also reported to be helpful Recently the synthetic preparation, *desoxycorticosterone acetate*, has been found to be a fairly satisfactory substitute for cortin It has the advantage of being less

expensive than the natural product which costs from about two to five dollars per patient per day It has the disadvantage, however, of sometimes upsetting the electrolyte balance to an extent that leads to edema and disturbed heart function Thorn has developed a technic for administering the drug in pellets beneath the skin In favorable cases a single implant has enabled patients to resume their customary activity over a period of months at a time There is some evidence that proper treatment may sufficiently relieve the strain on the adrenals as to permit their recuperation with occasionally, perhaps, a genuine cure of the disorder (Sevringhaus) In those cases that are due to cortical atrophy the use of pituitary *corticotropin* is theoretically indicated, but it has not been sufficiently used to permit any judgment of its practical worth The common immediate cause of death in Addison's disease is an intercurrent cold or other infection In the event of such mishap prompt and substantial increase in the hormone dosage is imperative

The existence of high grades of adrenal deficiency implies the existence of *lower grade deficiency* also The only escape from the implication is to assume that the adrenals follow some sort of all-or none law, or that the body has resources for compensation—resources which suddenly break down when over strained to a critical point Neither assumption has the flavor of good biology For lesser grades of cortical deficiency the old term *hypoadrenia* is sometimes used Many physicians doubt its existence, but such as do recognize it emphasize bodily weakness, lethargy, and low blood pressure as the most characteristic manifestations It is reported as occurring in all grades, from annoying fatigability to chronic weakness (asthenia) Various manifestations of "neurasthenia" may also be included in the picture That such inclusion is not entirely fanciful is indicated by Liddell and Hartman's demonstration that "experimental neuroses" in animals can be ameliorated by the use of cortin Perhaps the best test of whether the adrenals are involved in such cases is to determine whether lasting improvement can be brought about by administering cortical

hormone Some physicians have reported considerable success in such treatment In so far as the symptoms are of a "neurasthenic" order, however, the element of suggestion has to be taken into account in appraising the results

There are several other conditions in which the empirical use of cortical extract has been claimed to be of value Among these are muscular dystrophy, muscular atrophy, intestinal intoxication in babies, vomiting of pregnancy, and Paget's disease of the bones Generally speaking, in none of these disorders has satisfactory evidence of pathological disturbance in the adrenal glands been forthcoming Rather generally, however, the microscope does disclose evidences of disturbance in these glands following acute infections and severe burns Correspondingly, in these latter cases cortin has been reported to be of considerable use in hastening convalescence

Overactivity of the adrenal cortex may appear in several clinical guises The condition may arise from either simple hypertrophy (hyperplasia) of the glands or from the development of tumors—especially *hypernephromata* Theoretically, overactivity of the cortex should result in manifestations the precise opposite of those of Addison's disease or of experimental adrenal deficiency These would include exaggeration of growth and development and of sexual maturity and vigor As a matter of fact, it is in the sex field that the manifestations of hyperactivity of the cortex are most often recognized

Occasionally infants are born whose sex is curiously problematic. They appear to be both male and female The condition is known as *pseudohermaphroditism*, a term coined from the names Hermes and Aphrodite Actually the infants begin existence as girls but acquire a superimposed condition of *pseudomasculinity* The ovaries and uterus are indubitably feminine but the external genitalia become transformed toward the male type The victims may go through life without ever discovering the nature of the grim joke that has been played upon them In one classic instance the subject, under the delusion that she was a man, at the age of twenty-seven years

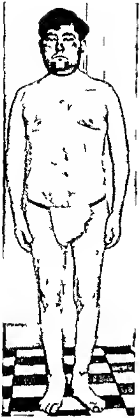
married another woman It was not until an autopsy was performed at the age of fifty nine, when ovaries instead of male sex glands were found, that the nature of the case was understood The pair had actually, though ineffectively, carried on a sort of sex life Such cases present, of course, many difficult psychological problems

For many years pseudohermaphroditism has been ascribed to overactivity of the adrenal cortex during the formative period before birth, though satisfactory objective evidence of the participation of the adrenals in the masquerade was usually lacking Actual enlargement of the cortex occurs in only about 14 per cent of the cases (Levy Simpson) More recently, evidence from the use of the fuchsin staining technic indicates that the cortex in such cases includes an abnormally high proportion of sex hormone secreting cells

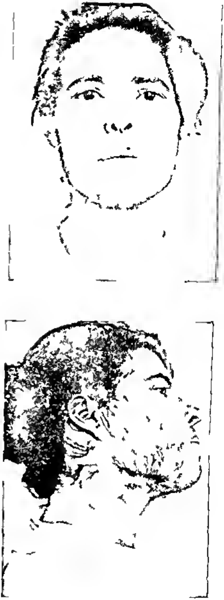
When overactivity of the adrenal cortex arises after birth a more sharply defined clinical picture is seen The condition is known as *adrenal virilism* (*pubertas praecox*, *adreno genital syndrome*) It is characterized primarily by precocious growth and sexual maturity, although in the individual case either one of the conditions may be inconspicuous or entirely lacking

In the earlier medical writings are recounted several instances of pubertas praecox which can now plausibly be ascribed to cortical overactivity, though this was not recognized at the time It is written of Craterus, brother of Antigonus "the subject was an infant, a young man, a mature man, an old man, was married and begat children and all in the space of seven years" Pliny the Elder (23–79 A D) quoted an older account of the son of Euthymenes, who "in three years grew to be three cubits or four and a half feet high, but he was in his gait slow and heavy, and in his wit as dull and blockish, howbeit in the time overgrown he was and his voice changed to be great, and at three years he died suddenly of a general cramp" In 1747, Mead reported to the Royal Society of London the case of a patient who was "remarkable for his bulk and height, who had acquired the external marks of puberty at the age of

Photograph showing in unusual degree the skin pigmentation of Addison's disease Courtesy of Dr Robert C Moehlig



(Left) *Case of excessive hair growth (hirsutism) ascribed to tumor of the adrenal cortex The patient's blood pressure was very high and he suffered from muscular wasting (myasthenia) From Blumer's* Bedside Diagnosis, *courtesy of Dr Hans Lisser and the W B Saunders Co*



(Right) *Adrenal virilism Photographs of a woman of 38 suffering from tumor of the adrenal cortex The hair growth had begun 15 months previously and menstruation ceased 8 months before From Blumer's* Bedside Diagnosis, *courtesy of Dr Hans Lisser and the W B Saunders Co*

one year When he died at the age of five he had the appearance of a venerable old man" In 1808, White described in considerable detail the case of Philip Hogarth in whom signs of puberty began at an early age At birth he had a full crop of hair At the end of a year his hair had grown to a great length and he was "pale and ugly in appearance" Unmistakable signs of sexual maturity had appeared and his voice was changing "On first view of the boy, the manly character expressed was extremely striking His voice was like that of a young man of sixteen years, his laugh was loud There was an odor emanating as that of an adult His height was three feet, two inches and he weighed forty seven pounds, i e, at two years At three years his height was three feet, four and a half inches and his weight fifty-one and one fourth pounds" The physician was impressed with his mental precocity "Many of his observations and inquiries appeared to have been the result of mature reflection It must, however, be observed that his general character was marked with a considerable mixture of childish playfulness He was mild and not easily provoked to anger When, however, his rage was excited, it was not expressed in the usual manner of children but by a lowering of the eyebrows, the shaking of his head and with his uplifted fist He had talent for music and sang with correctness"

Apparently the first American case reported was that of Stone in 1852 The lad, whose father had shown a similar condition, at the age of four appeared to be ten years old He was four feet tall and weighed seventy pounds His sexual organs were fully developed

Objective evidence of adrenal involvement is lacking in all these earlier instances, but in the more recent cases such involvement has often been demonstrated either at operation or at autopsy One of the most striking of these is that of Fraser, reported in 1940, apparently the youngest authenticated case on record Until the age of six months development had been normal, but at the age of one year extreme virilism was marked The penis had enlarged rapidly, the prostate had reached the

size of a walnut, and erections were almost constant Mastur bation was frequent Pubic hair had developed and the acne of puberty had appeared on the face, which seemed very mature for the age The voice was deep pitched The hands were greatly enlarged and muscular development was marked The bony development was in advance of the age and body weight was excessive The appetite was voracious The teeth had come in prematurely The patient was mentally retarded for his age, was bad tempered, and difficult to manage His actual age was twelve months, his dental age three years, his bone age five years, and his sexual age eighteen years More sex hormone was found in his urine than in that of an average man That this hormone was of immediate adrenal origin was sug gested by the fact that the size of the testes was normal for the age, only the penis and prostate marking the sexual precocity An exploratory operation revealed a tumor the size of a golf ball above the right kidney Its removal was postponed for six months and following a second operation the child died At autopsy the bodily organs in general were found to be normal

The condition of adrenal virilism may arise at any age and in either sex In *girls* and *women* its manifestations depend to a considerable extent upon whether or not puberty has been reached At any age, however, the disorder amounts to super imposing masculinity upon the feminine structure and tem perament When the disease begins in *infancy*, premature growth as well as sexual precocity (pubertas praecox) may be seen At first the precocity may include some feminine fea tures, such as uterine bleeding, but as a rule the masculine ele ments in the picture predominate from the first The little girl may develop a beard and mustache and show masculine distribution of the body hair, and, with this, a deep voice and athletic type of muscular development Hypertrophy of the clitoris is common Skeletal growth is advanced and the body may attain adolescent proportions even in infancy There may

be obesity, early appearance of the teeth, and marked physical strength

When the mishap arises later in *girlhood* there occurs not only failure of the feminine changes of adolescence, but also active masculinization The hair is of the male type and distribution The primary and secondary sexual organs fail to develop except that the clitoris hypertrophies The ovaries are cystic or sclerotic Menstruation fails to occur, or at best is irregular from the first and gradually ceases within a few years The uterus remains small The contour of the body as well as the bony framework and muscular development are masculine, with narrow hips and broad shoulders The larynx is large and the voice rough and husky Tragically, the young women may remain psychologically feminine and yearn for the normal romance which their hard fate denies them

When the virilism arises in *adulthood* the most striking changes are excessive hairiness, massiveness of the musculature, regression of the sex organs with hypertropy of the clitoris, menstrual irregularities, ending in amenorrhea and sterility and gradual disappearance of the feminine configuration

Virilism may arise not only from abnormality of the adrenal cortex, however, but also from disorders in the pituitary, the pineal, and, rarely perhaps, the thymus glands In males it may be due to primary tumor of the testes and in females to a tumor of the ovary known as *arrhenoblastoma* The condition of pituitary basophilism, or Cushing's syndrome, which will be discussed in a later chapter, also includes numerous of the features of adrenal virilism

When the adrenal is at fault it is possible at times to palpate a tumor externally or to outline it by use of the X rays after injecting the body cavity with air, but in order to identify the condition direct inspection is usually required In suspected involvement of the adrenals an exploratory operation is advisable because the tumor may be a dangerous *hypernephroma*,

removal of which may be lifesaving Operation may disclose the tumor in or near the adrenal proper But sometimes merely enlargement of the cortex on one or both sides is found Under the microscope merely a superfluity of cortical tissue may be seen, but in some cases it is possible to demonstrate the presence of an excess of fuchsin-staining (x zone) cells Another diagnostic resource is to assay the urine for its sex hormone content Either androsterone, adrenosterone, or other sex stimulating products may be found

The *treatment* of adrenal virilism, in so far as treatment is possible, consists usually of surgical removal of the offending tissue When the disturbing element is a discrete tumor the surgery is not too formidable, but when it is a generalized enlargement operation is fraught with danger When both glands are enlarged, attempts to reduce the redundant tissue are likely to result in what amounts to acute Addison's disease, with early death In a few instances, however, simple removal of one of the adrenals has been followed by amelioration of the symptoms If this is attempted the surgeon should, of course, assure himself that the other gland is present and offers promise of functional integrity Theoretically, adrenal virilism of women might be treated by giving enough female sex hormone to overcome the masculinizing influence, but most attempts that have been reported have been unsuccessful

In so far as masculinizing hormone may be produced in specialized (androgenic) cells of the cortex, the possibility exists that these alone may be affected, leaving cortin production unchanged On the other hand, overdevelopment of the androgenic cells may be accompanied by, or even may cause, atrophy of the cortin producing cells with corresponding degrees of ordinary adrenal deficiency A few cases have been reported in which individuals have shown both adrenal virilism and Addison's disease simultaneously

As was pointed out earlier, research chemists have obtained from the adrenal cortex not only masculinizing hormones but also the feminizing hormones, estrone and progesterone It

follows, therefore, that a clinical condition antithetical to virilism, i e, *adrenal feminization*, might arise In 1940 eight such cases had been reported An instructive instance is that recorded by Holl in a forty four year-old athlete His sex life had been vigorous He was married and had two sons Within a period of two years his breasts underwent development until they resembled those of a woman The external sex structures decreased in size and both sex desire and potency went into abeyance He gradually gained weight and the body hair became sparse His features took on a feminine appearance At operation a tumor of the adrenal was discovered and removed Within a week remasculinization began The breasts receded, the excess weight was lost, and the face regained its masculine characteristics Within a month the sex organs had regained their former size and sexual activity was resumed

CONTROL OF ADRENAL FUNCTIONS

The importance of sympathetic nerve impulses in the regulation of adrenin discharge from the medulla has already been stressed Whether the cortex is subject to similar nervous control is not known An important factor in the regulation of the cortex is a hormone produced by the anterior lobe of the hypophysis This has been named *corticotropin* or corticotropic (adrenotropic) hormone There is some evidence that a *medullotropic* hormone is also produced The evidence for the existence of corticotropin is essentially that destruction of the hypophysis results in marked atrophy of the adrenals and that restoration of the structure can be brought about by special pituitary extracts The evidence now available indicates that clinical adrenal deficiency can result from either local destruction of the glandular tissue or from deficiency of the adrenotropic hormone It is possible that such a lack may even be a factor in cases in which the adrenals are directly affected by disease processes, they having been rendered vulnerable by preceding lack of adrenotropic support

BIOLOGY OF THE ADRENALS

An appraisal of the biological significance of the foregoing data as a mass picture presents no little difficulty The occurrence of adrenals throughout the vertebrate group of animals indicates, of course, that they play an important role in the physiologic scheme of things Since they are as prominent in the higher as in the lower forms, they cannot be classed as vestigial carry-overs from any earlier plan of organization Neither are they among the category of redundant mechanisms that overspecialized forms sometimes develop in the last stage before their evolutionary extinction What survival value, then, have these structures that has led to their preservation in the evolution of the higher animals?

As far as the adrenal medulla is concerned, a sufficient *raison d'être* is their aid in integrating the organism to meet emergency conditions In this regard, the medulla serves to reinforce the sympathetic nervous system as the agency by which the body is transformed into a mechanism fitted for vigorous activity while leaving it adjusted during periods of quiet existence to pursue the even tenor of its ways The animal that can bring to bear effective spurts of energy when conditions demand but remain calm at other times has an obvious advantage in competition with enemies less fortunately endowed

The adrenal cortex, however, presents a problem less easily understood The fact that this part of the gland is at its relative maximum size during the early fetal period, when growth and development constitute the major activities of the organism, suggests that it plays an important role in connection with such processes It is further to be noted that waves of cortical activity occur during pregnancy and during the breeding season, when special demands are put upon the organism But even so, the mechanism might seem to be superfluous, at least during the fetal period, when the tissues have a highly developed intrinsic growth impulse The inheritance of such an impulse and provision for its gradual extinction with the

achievement of metabolic equilibrium in adult years might seem to meet all the needs of the situation as regards growth Since the gland continues to manufacture growth promoting secretion during the adult period, and in both sexes, it may be presumed that the hormone in question has functions other than the promotion of growth One such plausible function is the promotion of muscle metabolism

Even more puzzling, perhaps, is the relationship of the glands to sugar metabolism Innumerable instances could be cited throughout the animal and vegetable kingdoms of forms that metabolize carbohydrate effectively without the aid of a cortical hormone A priori, in higher animals the fatal dependence of this fundamental metabolic process upon an accessory organ would seem to be an unnecessary peril

The relation of the adrenal cortex to the evolution of the sexual function again seems paradoxical Puberty is primarily dependent upon an evolution of the primary sex glands themselves Why should a secondary control by the adrenal cortex have been imposed? The advantage is by no means apparent Furthermore, why should the adrenal exert a predominantly masculinizing effect when half the possessors are female?

The evidence of Secker that cortical extract promotes the activity of the sympathetic nervous system may afford the key to much of the mystery of this structure The sympathetic system plays a highly important role in the regulation of the vegetative processes of the body, generally This system, in turn, has its own metabolic processes and an agent to promote these could have far reaching adaptive significance Possibly further researches on this relationship will bring substantial clarification of the existing incertitude

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III. THE THYROID GLAND

EARLY STUDIES

Quis tumidum guttur miratur in Alpibus—"Who wonders at goiter in the Alps!" These words, written by Juvenal nearly two thousand years ago, indicate that the thyroid was a structure familiar to the ancients Beyond the existence of the gland, however, and its liability to goitrous swelling the early knowledge did not go During the earlier centuries of our era numerous theories about the thyroid were proposed, but no one after the Greeks descended to the unfashionable procedure of grubbing for facts Some writers regarded the thyroid as a protective device to keep the throat warm, "to cherish the vocal chords" Others ascribed the gland to the aesthetic impulse of the Creator, who established it for the purpose of rounding out the neck in a beautiful contour The theory that gained most favorable currency in the nineteenth century was that the thyroid, like the adrenals and various other endocrine structures, had no significance except during the prenatal stage of existence—and what it did even then was a complete mystery

The thyroid was discussed by the Renaissance anatomist Vesalius (1543), but received its present name about a century later from Wharton The term is derived from a Greek word meaning "shield shaped" Meckel (1806) asserted that the thyroid gland often swells at critical periods in the sex life of women such as pubescence, menstruation, defloration, or pregnancy In this connection it is interesting that the Romans made a practice of measuring the necks of brides as a test of

prenuptial virginity There is no evidence, however, that they recognized the part which the thyroid might have had in the matter In the sixteenth century, Paracelsus noted the prevalence of goiter in the Salzburg region and, in agreement with modern writers, attributed it to defective mineral content of the drinking water He noted, too, that endemic goiter coexisted in the same locality with cretinism or myxedema and that goiter is often associated with idiocy A foreshadowing of more recent knowledge of the importance of iodine in relation to the function of the thyroid appears in the teaching of Roger of Palermo (1180) that there is something in the ashes of sponges and seaweed that is beneficial to goiter

The foregoing constitutes essentially all that was factually known until about a century ago The first to undertake research on the function of the thyroid was Schiff of Geneva (1858) He removed the glands from a series of animals and found that death soon followed Little attention, however, was paid to the new fact Physiologists at that particular time, as Meltzer points out, had neither any great interest in biologic researches as we know them today nor confidence in their results It was the fashion of that time to try to explain all the phenomena of life in terms of inanimate mechanism

For the next additions to our knowledge of the thyroid functions clinicians rather than professional scientists are to be thanked In 1873, Sir William Gull, the surgeon, reported the cases of five middle aged women who were marked by puffy faces, bulky forms, and physical lethargy Five years later Ord, another British physician, had opportunity to make a post mortem examination of a patient showing the same symptoms He noted that the thyroid gland was shrunken (atrophic) and that the general puffiness of the external layer of the body was due to the accumulation of mucilaginous-appearing material beneath the skin He therefore named the new disease *myxedema*, which is Greek for "mucoid swelling"

The next step in discovery came when the introduction of

antisepsis by Lister emboldened surgeons to carry operative procedures into regions of the body which up to then had been essentially inaccessible They now began to treat goiters by radical operation Reverdin of Geneva reported a few such operations in 1883 and during the same year Kocher of Bern, subsequently a world famous authority on goiter, gave a more extensive report which included a discussion of the aftereffects of complete removal of the gland He emphasized especially the profound interference with nutrition In this same year Semon called the attention of the Clinical Society of London to the similarity between the symptoms of spontaneous myxedema and those which follow surgical removal of the thyroid He suggested that the gland might be of fundamental importance to life

Stimulated by the keen interest that had arisen in the clinical aspects of thyroid function, Schiff was led to repeat and extend his earlier experiments, he, too, now having the benefit of antiseptic technic He showed that complete destruction of the thyroid in dogs was commonly followed by death and that the symptoms somewhat resembled those following complete removal of goitrous glands in man The earlier work was confused, however, by the fact that the parathyroid glands were often unknowingly removed with the thyroid and symptoms of deficiency of both glands appeared together

The scene then shifted from Switzerland to Germany Bruns had noted in the literature a report of the case of a boy from whom a goitrous thyroid had been perilously removed in the pre antiseptic period The lad had managed to survive the operation and was then nearly forty years old, but in size and appearance he resembled a mentally and physically backward boy Thus, the conviction was deepened that the thyroid plays an important role in body metabolism The final logical step in proof of that thesis was taken by Schiff, who found that if a piece of living thyroid tissue was transplanted into the body cavity of the animal from which it was taken the remainder

of the gland could be sacrificed without harm—final proof that the disturbance following thyroidectomy was due to the lack of gland tissue and not to operative injury as such

Schiff's new evidence was put to clinical use by von Eiselsberg, who reported the first case of thyroid grafting in man It was found that, although the symptoms of thyroid deficiency could be held in abeyance for a considerable period, the grafts were ultimately absorbed and the symptoms reappeared It was thus seen that the implantation amounted, in effect, merely to the injection of thyroid material—a procedure that likewise proved to be successful The next simplification, that of giving thyroid substance by mouth, was introduced in 1891 The first patient to be successfully treated by the new method was that of Murray She died in 1919 at the age of seventy four, her health having been maintained on thyroid treatment for twenty-eight years, during which time she had consumed the glands of several hundred sheep

THE ORIGIN AND STRUCTURE OF THE THYROID

The thyroid gland is found in all vertebrate animals from the lowest fishes up to man In the human embryo as well as in the lowest vertebrates, which the embryo resembles in many respects, the thyroid in its earliest stage is represented by a protrusion from the floor of the mouth cavity A vestigial reminder of this origin persists in man throughout life as a minute dimple at the back of the tongue, the *foramen caecum* In *embryological development* the future gland first appears as a thickening groove in the floor of the mouth cavity, this can be seen as early as the third week of fetal life By the time the embryo is a fourth of an inch long, the forming thyroid tissue has been pinched off and the cavity closed up The connection with the mouth may persist, however, in some cases as the *lingual duct*, a structure from which cysts and fistulas sometimes arise later in life

By upward and downward growth, the embryonic thyroid

finally takes its ultimate position as a pair of *lobes* on the two sides of the trachea at the root of the neck with a connecting band of similar tissue, the *isthmus* In thin people the isthmus can be seen as a ridge that moves up and down under the skin with swallowing In the adult man the thyroid weighs about an ounce and in the woman it is slightly larger It has a profuse blood supply, receiving a pair of arteries from the external carotids, another pair from the subclavian arteries (the *superior* and *inferior thyroid arteries*) and a smaller median artery, the *thyroidea ima* Within the gland the blood is distributed mostly through networks of capillaries that surround the follicles The gland is abundantly supplied also with veins and lymphatics It is estimated that the entire volume of the blood passes through the thyroid gland about sixteen times each twenty four hours The *nerve supply* is partly sympathetic from the cervical trunks and partly parasympathetic from the vagus via the superior laryngeal nerve

In *microscopic structure* the thyroid gland of man or other higher animal presents a picture distinct from that of any other tissue in the body It consists of many tiny sacs (*vesicles*) lined with secreting cells and filled with a jellylike substance (*colloid*) derived from the lining cells When the thyroid is in a resting state the colloid accumulates in the vesicles and the lining cells assume a flattened form In conditions of overactivity the colloid is partly or wholly absorbed and the vesicular cells become elongated (*hyperplastic*) They may also increase in numbers to such an extent that the tissue is thrown into folds within the vesicle cavity The colloid apparently serves as a menstruum in which the hormone of the gland is stored when it is being formed in excess of the immediate needs When increased need arises it can be absorbed into the blood stream to augment the supply discharged from the thyroid cells directly into the circulation

The thyroid reflects changes in the *nutritional state* of the body Excessive consumption of meat, especially of liver, leads to overactivity This, according to some authors, is followed by

exhaustion of the gland and accumulation of colloid in its vesicles Sea food, on the other hand, with its high iodine content, causes reduction in the size of the gland just as do iodine salts themselves Fats also have a tendency to cause thyroid hypertrophy Diets in which calcium and phosphorus are out of balance—and especially when iodine is deficient—also cause enlargement On the other hand, undernutrition causes involution of the thyroid with a decrease in the size of the vesicular cells, diminution of blood supply, and increase in the colloid and iodine store Lack of vitamins in the diet is reported to have a similar effect The thyroid enlarges and presents microscopic signs of increased activity during cold seasons and, as previously stated, during physiological periods of special stress, such as puberty and pregnancy The evidence that emotional strain may cause marked overactivity of the thyroid is also rather convincing

From the foregoing evidence it could confidently be deduced that the thyroid gland has a special relationship to nutrition and energy release Such actually is the case In the presence of normal thyroid secretion both proteins and fats, and to some extent carbohydrates as well, have a stimulating effect—*specific dynamic action*—upon the body metabolism When the thyroid hormone is deficient this stimulating influence of the food is materially lessened, while thyroid feeding restores it

THE THYROID HORMONE—THYROXINE

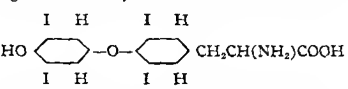
That a special relationship exists between the thyroid gland and the element iodine has long been known The entire body of a human adult contains between twenty and fifty milligrams of iodine, an amount less than that in ten drops of the standard medical iodine solution Of this quantity the muscles contain half, the skin one tenth, and the skeleton one seventeenth As would be assumed, therefore, the amount in circulation in the blood is very small, amounting to about one one hundredth of a milligram per cent (a milligram is one sixty fifth of a grain)

Of the total amount of iodine, the thyroid gland normally contains about one fifth, though that structure makes up only about one five hundredth of the total body mass Thus its iodine concentration is a thousand times that of the muscle It is interesting that the endocrine glands in general have propor tionately about four times as much iodine as have other body tissues, but the significance of this fact is not known

Baumann (1895) first showed that iodine in a firm organic combination is a normal constituent of the thyroid tissue He treated the gland substance with sulphuric acid and derived a brownish powder containing about 9 per cent of iodine This he called *iodothyrin* It was supposed for a time to be the true active principle of the gland Subsequently, Oswald showed that the colloid material of the gland is rich in iodine From this source he obtained two protein substances, *thyroglobulin* and *iodothyroglobulin* The latter is a composite mole cule containing both diiodotyrosine and thyroxine as integral parts Iodine has been found in the human thyroid as early as the third fetal month In postnatal life the amount varies with the season, being relatively low in the spring and high in the late summer Thyroid tissue has a special ability to select iodine from fluids circulated through it As can be determined by using radioactive iodine, a given injection can be completely taken up within fifteen minutes This special affinity is shown also when iodine is fed to a pregnant mother, in which case it is rapidly stored in the thyroid of the fetus

After the work of Baumann and Oswald, the next major step in the isolation and study of the thyroid hormone was made by Kendall in 1916 By means of alkaline hydrolysis he succeeded in deriving a crystalline compound, containing 65 per cent of iodine and having numerous of the same effects throughout the body as does thyroid substance itself This com pound he named *thyroxine*, a word coined from selected letters of the chemical label—trihydro-triiodo-oxyindole propionic acid This, he believed, represented the true hormone Ten years later Harington and Bayer (1927) improved the method

of extraction and were able to secure better yields. They determined the empirical formula to be $C_{15}H_{11}O_4NI_4$. The substance is a tetraiodo substituted derivative of the p hydroxyphenyl ether of tyrosine or tetra iodothyronine. Its molecular arrangement is shown by the structural formula:



Whether this material represents the true thyroid hormone is still a matter of dispute. Marine believes that the true substance is the iodothyroglobulin of Oswald and that thyroxine is merely the chemical group within the molecule that gives it its activity. In his earlier studies, Kendall had obtained another iodine containing substance which was without hormonal activity and which Harington subsequently showed to be di-iodotyrosine. By a special chemical procedure, using pepsin to catalyze the reaction, Salter has been able to obtain an active material, presumably thyroxine, from diiodotyrosine. The two substances, thyroxine and diiodotyrosine, seem to exist in a balanced state, the equilibrium point of which varies under different physiological or pathological conditions but with the greater part of the iodine held in the inactive fraction.

Normally, according to Salter, the thyroxine output of the thyroid in man is about one milligram each three days. When the gland is secreting hormone at full capacity its total iodine reserve may be depleted to less than a tenth of its ordinary amount and the thyroxine discharged as rapidly as formed. A fact which indicates that the manufacture of thyroxine is not as simple a process as ordinarily depicted is that various proteins such as casein, when combined with iodine and treated with alkali outside the body, yield compounds similar to thyroxine. Furthermore, serum albumin, when iodized even

without alkalination, is an effective remedy for thyroid deficiency

The biological significance of the thyroid hormone centers in its relation to *metabolism* In 1893, von Muller discovered that overactivity of the gland causes increased expenditure of nitrogenous body materials (proteins), as shown by the end products excreted in the urine Later researches have shown that carbohydrates and fats also share in the increased oxidation That the physiological processes generally are stimulated by the thyroid hormone is indicated not only by the increased oxidation rate, but also by the wasting of tissues and increased reactivity of the nervous system

EXPERIMENTAL THYROID DEFICIENCY

Much of our knowledge of thyroid physiology has been derived from careful study of the effects of removal of the gland As Magnus Levy first showed (1895) in human subjects, thyroid deficiency brings about depression of the metabolic processes Thus the oxygen-consumption rate (*basal metabolism*) is reduced—in severe cases as much as 40 per cent The rate can easily be restored to normal by feeding gland substance or thyroxine The metabolic level can be studied also in the tissues directly by noting the rate at which they consume oxygen when taken from the body and preserved in warm salt solution—e g, in a "Warburg chamber" By this technic it is found that the metabolic rate progressively falls for days or weeks after the thyroid has been removed Conversely, when thyroid substance is fed the tissues show an augmented oxygen-consumption rate

Thyroxine has a marked influence not only on immediate oxidative reactions, but also on the processes by which *maturation* and *differentiation* are brought about When the thyroid tissue is removed from frog larvae (tadpoles) they are unable to complete their development and change into frogs On the

other hand, it is possible, as Gudernatsch has shown, by feed
ing small amounts of thyroid substance to tadpoles to mature
them so rapidly that they are unable to attain a normal size
Thus frogs no larger than houseflies have been produced In
deed, by the use of thyroid substance it is possible to improve
upon nature in at least one respect In the highlands of Mexico
lives a species of salamander (axolotl) that ordinarily suffers
such a degree of thyroid deficiency that it never changes from
the tadpole to the adult state Thus it continues from genera
tion to generation as a gill bearing larva By administration of
thyroid substance, metamorphosis can be readily induced and
nature's handiwork thus completed The metamorphosis reac
tion of tadpoles has been widely used as a test for the presence
or absence of thyroxine in extracts By the dilution technic it
can also be used for quantitative assays

When the thyroid is removed from young animals of higher
species, arrested development is manifested in a variety of
ways The cartilages are only slowly transformed into bone
The brain fails to mature and low intelligence is a common re-
sult The teeth are poorly formed and delayed in their appear
ance The sex organs remain small and commonly fail to ac
quire active functions The tone of the muscles remains slack,
a fact which accounts for the loose jointedness and the pro
truding abdomen that are characteristic of thyroid deficiency
The skin is thick and poorly nourished and the hair is coarse,
sparse, and dry Even though the individual lives well into
adult years normal size is not attained, hence thyroid deficiency
is one cause of *dwarfism* The temperature of the body is char
acteristically below the normal level

The chemical processes of the body upon which growth and
functioning depend are stepped down to not much more than
half the normal rate Because of the depression of the com
bustion processes there is likely to be an accumulation of body
substances with resulting *obesity* This relative oversize is often
aggravated by accumulation of water in the tissues The repara
tive processes of the body are defective and wounds and frac

tures heal slowly The vitality of the blood forming organs is depressed, leading to a condition of anemia

A large part of what is known about thyroid deficiency can be deduced from the broad statement that complete deprivation of the hormone slows down the chemical processes of the body Apparently all living cells are affected—including those of the various other endocrine organs That statement means that not only is development retarded but that the incomplete tissue apparatus is further hampered by general inefficiency of such elements as are present A fact, however, which necessitates caution in generalizing is that some processes—for example, reproduction—may not reach any functional activity at all

Many more details could be added from the literature of animal experimentation, but they are closely paralleled in human cases in which thyroid function is depressed and will, therefore, be set forth in the subsequent section on clinical disorders

CLINICAL DISORDERS OF THE THYROID

Hypothyroidism

Thyroid deficiency as it appears in human beings may be seen at any age from well before birth to the senile period of life It may be due to actual injury of the gland by accident or disease or too much of it may be inadvertently removed in an operation Simple atrophy may also be a cause High degrees of functional deficiency can arise from lack of iodine in the food

Hypothyroidism in infancy and childhood may first be considered In some regions of the world where iodine is deficient in the soil—hence in foodstuffs grown on it—pregnant mothers suffer especially and are likely to give birth to children with defective thyroids The glands are prone to remain undeveloped or may easily undergo atrophy and fibrous degeneration The resulting disease is known as *cretinism* When

the thyroid deficiency arises after the child is born, but while it is still very young, the disorder is known as *infantile myxe dema* Commonly the disturbance is less profound in the latter condition, but in either case the child is a puffy, misshapen be ing with thick, protruding tongue In consequence, he is often unable to nurse and must be fed artificially The skin is dry and cold to the touch It feels thick and seems lifeless The hair is harsh and dry and falls out readily Even the eyelashes may be sparse or lacking The nails are thin and brittle The teeth are slow in appearing and have little vitality, even with the best of dental care they are frequently lost The face is pale and puffy and completely lacking in animation The upper eyelids are thick, giving the child a sleepy appearance, the eyes are dull and lusterless The hands and feet are broad and clumsy The bones of the head and face develop at disproportionate rates, leading among other things to a marked depression of the root of the nose, giving it a characteristic "saddle shape" The lips are thick and prominent and the mouth is often held partly open to give space for the oversized tongue The mus cles are limp and weak and flat feet may result, the shoulders droop and the abdomen sags The internal organs are slug gish, leading among other things to constipation The nervous system remains underdeveloped both structurally and func tionally and the intelligence grades from feeble mindedness to idiocy

> No type of human transformation [as Osler says] is more dis- tressing to look at than an aggravated case of cretinism It recalls Milton's description of the Shape at the Gates
>
> If shape it might be called, that shape had none
> Distinguishable in member, joint or limb,
>
> or those hideous transformations of the fairy prince into some frightful monster The stunted stature, the semi bestial aspect, the blubber lips, retrousse nose sunken at the root, the wide open mouth the lolling tongue, the small eyes half closed with swollen lids,

the stolid expressionless face, the squat figure, the muddy, dry skin, combine to make the picture of what has been well termed "the pariah of nature" Not the magic wand of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in helpless imbecility, an unmistakable affliction to their parents and to their relatives . .

In some instances the children at birth seem fairly normal, presumably because of having received a supply of thyroid secretion in the blood of the mother before their advent into the world, and, subsequently, in the mother's milk. At any rate it is not until after weaning that they acquire the typical myxedematous condition, but then it develops rapidly

The foregoing account relates only to children in whom the gland deficiency is almost or quite complete More commonly, however, thyroid deficiency occurs in lesser degrees *Partial deficiency* results in various combinations of the features mentioned and in differing degrees of completeness Fairly marked mental retardation and physical underdevelopment may occur in the absence of any of the other signs of childhood myxedema In particular, and deceptively, the basal metabolic rate may be recorded as normal—though it probably never actually is The correct diagnosis is often missed The part played by thyroid deficiency in such cases is revealed by the acceleration of growth, bone development, and eruption of the teeth that ensue when thyroid substance is given The possibility of a thyroid factor in mental retardation in children should never be ignored The handicap can usually be removed by simple medication Unfortunately, however, there are many causes for mental retardation other than thyroid deficiency and a considerable proportion of these cannot be corrected by any means now known

A condition often confused with childhood myxedema is the disorder known as *mongolian idiocy* or *mongolism* It is highly desirable that the condition be recognized for what it

is rather than for thyroid deficiency, if for no other reason than to forestall the raising of false hopes It is even more desirable, however, to avoid the blunder that is occasionally made of mistaking childhood myxedema for mongolism, and thus postponing or completely failing to institute proper treatment Success with thyroid medication is commonly as brilliant in the one case as it is ineffective in the other

Curiously enough, thyroid deficiency has afforded a favorite theme for more than one of the great Renaissance painters For example, the Court Dwarf of Don Baltazar Carlos, painted by Velasquez, was unmistakably a victim of childhood myxedema Some of the dwarfs of present day circus troupes fall in the same category, though their stupidity renders them unsuitable for anything but freak displays The intelligent midgets are either subjects of pituitary deficiency or victims of the little-understood malady, *achondroplasia*

Thyroid deficiency may make its first appearance in adult years when either disease or the scalpel of the surgeon sufficiently reduces the amount of functional glandular tissue Although it may occur at any age, *adult myxedema* is characteristically a disease of middle life There is some apparent tendency for the disorder to run in families The symptoms are generally similar to those of the childhood variety except that, growth having already been completed, only regressive changes are possible The onset of the disorder is usually slow and insidious, requiring several years for its full blown development For some reason—possibly the greater stresses of reproduction in this sex—women are severalfold more prone to myxedema than are men Fortunately the disease is fairly rare, though more common than is ordinarily recognized In cases in which it is finally diagnosed, the patient has often passed through the hands of several physicians before the true nature of the malady is finally recognized—and this despite the fact that almost any medical student can give a good description of it

A characteristic of the disease is sensitiveness to cold The body temperature may be reduced by as much as three and a

half degrees Many subjects complain of cold hands and feet and admit the habitual use of hot water bags in bed They experience almost unbearable chilliness and often wear an astonishing array of extra clothing Lisser has reported a patient who customarily drove about in a closed automobile in the hot summertime, dressed in a heavy overcoat "The first sign of improvement gratefully acknowledged by the patient in response to treatment with thyroid extract is a feeling of 'thawing out,' an increased feeling of warmth"

As the disease develops, both the patient and his friends become aware of his increasing difficulty in mental activity He grows more and more forgetful and recalls only with difficulty the events of his past life He becomes unable to concentrate effectively on reading, thinking, or listening He loses his initiative and his capacity to reach decisions or to carry out plans

In keeping with the changes in the personality is the increasingly puffy, bloated appearance The skin becomes thick and doughy, even that of the eyelids being affected—a change that accentuates the appearance of stupidity The lips and tongue become thick as do the mucous membranes of the nose and throat, leading to a tendency to mouth breathing and snoring Thickening of the vocal cords lowers the pitch of the voice and the speech often shows a singsong intonation Despite a dainty appetite, the patients ordinarily do not lose weight and sometimes become quite obese Even though little food is consumed, still less is oxidized—a fact which accounts for the characteristic lowering of the basal metabolic rate In the cases of obesity in which the thyroid actually is at fault, treatment with gland substance is efficacious, but its use in other types of obesity is ordinarily not very effective If used overenthusiastically, as it must be, in such cases, to achieve slenderness, the medication may result in serious harm—especially to the heart

Among the symptoms of adult myxedema are chronic headache and constipation Most of the patients complain of tiring

easily The fatigue often takes the form of breathlessness which, in turn, is dependent in part upon poor nutrition of the heart muscle The pulse is generally slow and sometimes strik ingly so The kidney functions tend to be sluggish with re sultant accumulation of waste products in the blood Moderate grades of anemia are rather characteristic In the sex sphere impotence is common in men and menstrual irregularities in women, the flow is characteristically excessive but may be scanty or even entirely suppressed Thyroid deficiency is a sig nificant factor in sterility The defect may exist in either would be parent

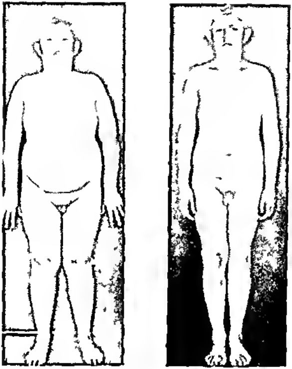
In addition to the sluggish, myxedematous type of de ficiency, as just described, some writers also emphasize another "thin, irritable, *non-myxedematous*" type The subjects, far from being phlegmatic, are overresponsive to environmental annoyances The causal relationship of the thyroid deficiency to the condition is indicated by a marked diminution of the basal metabolic rate Under thyroid medication the basal rate and the weight are normalized and placidity of disposition is restored Even in the myxedematous type of deficiency, how ever, truculent irritability rather than lethargy may occur—as was noted in the classic report of the British Myxedema Committee as early as 1888

As in the childhood forms, the disease process in adults may be arrested at any stage, giving rise to all degrees of thyroid deficiency from slight abnormality to complete incapacitation There are many victims of *lesser degrees* of thyroid deficiency in whom the diagnosis is seldom made They can best be de scribed, in the words of McLester, as suffering from "general poor health" They show lack of endurance, referred to as "chronic nervous exhaustion" and manifested by inability to resist or endure physical and mental strain The reasoning power, as such, is impaired little, if at all, but the subject is incapable of consistent mental effort and is lacking in initiative Numbness or vague pains in the arms and legs, occasionally chronic joint pains, and frequently constipation and vague di

(Upper left) *A case of infantile myxedema in a child 2 years, 10 months old*

(Lower left) *Same patient a year later after 10 months of thyroid treatment Courtesy of Dr Jas A Wood, Good Samaritan Clinic, Atlanta, Ga*

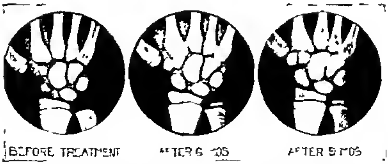
(Upper right) *Don Baltazar Carlos and his Dwarf Painted by Velasquez Original in Museum of Fine Arts, Boston The "saddle nose," pudgy features and dwarfism are characteristic of childhood myxedema*



A case of combined thyroid and pituitary deficiency in a boy of 12 years The same patient a year later after treatment with thyroid substance and anterior lobe pituitary extract Initial weight, 174 pounds, after treatment, 140 pounds Initial height, 61 5 inches, after treatment, 63 5 inches Courtesy of Dr E Kost Shelton

A case of Mongolism with thyroid deficiency in a girl of 11 years The same girl at 15 after four years of thyroid treatment Courtesy of Dr Jas A Wood, Good Samaritan Clinic, Atlanta, Ga

Hypothyroid obesity Note the characteristic "fat pads" of the neck and over the shoulders The basal metabolic rate was 26 per cent below normal From Blumer's Bedside Diagnosis, *courtesy of Dr. Hans Lisser and the W B Saunders Co*



Bone development in a case of thyroid deficiency. X ray photographs of wrist of a boy of 9½ years and at intervals during thyroid treatment Bone development progressed 2 years in 9 months of treatment. Courtesy of Dr. E. Kost Shelton

gestive disorders, are complained of Occasionally the subject is overweight His muscles are rather small and flabby He often appears to be tired, but in conversation he may brighten up and for a time show normal interest and enthusiasm His circulation is poor, the pulse slow, and the blood pressure low He is often mildly anemic The kidney functions are depressed and the urine often contains albumin, a fact that sometimes leads to a diagnosis of nephritis and even to treatment for this disorder The cause of the "poor health" often remains undiscovered—a similar state may result from numerous causes—but the key to the situation when the thyroid is at fault is a depression of the basal metabolic rate The condition yields readily to thyroid treatment but never to the good advice with which the "neurasthenic" victim is plagued Ordinarily, under the microscope, the thyroid gland appears to be approximately normal—a fact which leads some clinicians to the conclusion that the condition is not one of true thyroid deficiency, but is one in which the patient merely responds satisfactorily to thyroid substance as a general tonic The fact that the patient responds to small doses of the material, on the other hand, is cited as evidence of genuine hormone deficiency This might arise, perhaps, from fatigue of the thyroid cells or from inadequate stimulation through the controlling mechanisms In any case, from the standpoint of the patient, it is a distinction without a difference

The effects of thyroid deficiency on the *personality* vary widely from case to case The subjects are rather commonly depressed in mood, dissatisfied with life, and distrustful of their associates The depression may go on to the extent of a genuine psychosis In severe cases delusions and hallucinations of hearing, sight, smell, and taste may occur The patient may find himself uncontrollably impelled to bizarre conduct In the most severe cases confusion is also seen In short, a condition may develop that is clinically indistinguishable from the ominous psychosis, dementia praecox It is interesting that Hoskins and Sleeper have reported the occasional occurrence

of recognizable degrees of hypothyroidism in this psychosis and have found that significant improvement is not infrequently seen in such cases following thyroid medication There are recorded in the literature several instances of complete cure of apparently genuine dementia praecox under such treatment —but many failures have also occurred

The *diagnosis* of hypothyroidism is often obvious from the association of defects to which it gives rise There exist, however, many atypical and borderline cases that may require special studies for their identification The most common diagnostic procedure is to determine the basal metabolic rate Any rate below 85 per cent of calculated normal is suspicious In certain cases, however, in which tenseness or restlessness is a symptomatic feature, the true basal rate is difficult to determine, implying as it does composure of body and mind in addition to quiescence of the digestive system Even in ordinarily placid people false "basals" are frequently reported, because of failure to allay the suspicion of the subjects toward the technical procedures or other failures to obtain complete relaxation Thus, considerable degrees of metabolic depression may be overlooked and the trusting physician misled in his estimate of the case

In children, appropriate prolonged quiescence is usually difficult or impossible to achieve Recourse is then had to a study of the *bone age* in comparison with the calendar age The procedure is to make X ray photographs of the wrist and note the extent to which the cartilages have been transformed into bone In the higher degrees of thyroid deficiency a lag of several years may be found Another diagnostic method is to determine the concentration of *cholesterol* in the blood serum This may run normally as high as two hundred and seventy five milligrams per one hundred cubic centimeters, but in hypothyroidism twice as much More recently an *iodine tolerance* test has been introduced The technic, however, is exacting and can be carried out reliably only by those having special competence as well as adequate technical facilities As a matter

of practical clinical fact, often the best way to reach a diagnosis is by *therapeutic test*, noting how the patient reacts to a trial course of thyroid medication

In principle, the *treatment* of thyroid deficiency in any of the foregoing guises is easy Often, all that is needed to restore normality is to supply artificially a sufficient amount of the missing hormone Thyroxine may be used, but more commonly, less expensively, and quite as effectively, dried thyroid substance can be prescribed In actual practice little difficulty is usually experienced The chief danger is overdosage It is important that the diagnosis be made early and treatment instituted before irreparable secondary damage has been done The effects of thyroid medication may be very striking Thus a stunted child may increase as much as a foot in height in a year and may put on many pounds of weight—better results than have ever been achieved by pituitary growth hormone in the most favorable cases Similarly, delayed puberty can be corrected promptly and completely

The best guide to *dosage* is the basal metabolic rate Generally speaking, enough thyroid substance or thyroxine should be given to bring this up to the patient's own normal It is to be noted, however, that this is not necessarily the same as the theoretical normal Many people maintain robust health with basal rates ten to fifteen points below their calculated ideal, and ten points above this level is usually no handicap Basal rate determinations, however, are of relatively little use in determining the initial dosage Lawrence writes of a patient whose basal rate was 66 per cent of his calculated normal, which promptly normalized on a dosage of three grains daily In another patient, with only a 14 per cent depression of the rate, eight grains were required In general, it is desirable to begin with one grain a day or less and gradually increase the dosage until it reaches a level appropriate for the given patient. One tenth of a grain daily may be enough In this process of fitting the medication to the man the delayed influence of the drug must be kept in mind About three days is required for

any given dose to exert its maximal effect and about three weeks for this effect to wear off After preliminary orientation is secured, basal rates need not necessarily be determined at frequent intervals, the resting pulse rate may be used between times as an index of dosage The pulse becomes rapid or over responsive to environmental changes when the optimal dosage is overrun In any case, the pulse should be watched because individual overdosage may occur before the calculated basal rate is achieved

The impression is fairly widespread that thyroid dosage can be controlled by noting *weight changes* in the patient This is not necessarily true The first effect is likely to be a prompt loss of weight due both to absorption of the myxedematous deposits and excretion of water from the tissues generally This initial fall may amount to several pounds within a week If the patient is actually obese, the weight continues slowly to decline because of the burning of excess fat but otherwise it soon becomes stationary If, as is not infrequently the case, the initial weight is below normal, it may actually increase under thyroid medication—sometimes several pounds in a month A seemingly paradoxical effect sometimes seen is a brief drop in the weight—due to water excretion—followed by an increase, due to improved tissue nutrition

Another apparent paradox may be seen in the effect of thyroid medication upon *blood pressure* If this is low because of weakness of the heart muscle, the treatment commonly raises the pressure as the nutrition of that tissue picks up On the other hand, myxedematous infiltration of the body tissues sometimes so impedes the progress of the blood in the capillaries as to lead to chronic high blood pressure When the infiltration disappears under medication, the pressure recedes Thus, the tendency is to normalize the pressure whether it be initially high or low Often, no significant change occurs

One special *precaution* should be observed when thyroid treatment is begun in the more severe grades of deficiency in which the heart nutrition is seriously impaired The sudden

stimulation of the body wide metabolic processes may result in throwing an undue load upon the heart, which is slow to pick up the new pace that is required Symptoms of acute heart failure may then be alarming A not uncommon medical blunder at this point is to conclude that the medication is "toxic" to that individual patient and accordingly further to deprive him of the one thing that can give him substantial help The proper procedure in case of overdosage is to with hold thyroid for a few days, then to build up the dose at a gradual rate to permit the weakened heart to keep pace with other improvements It is also advisable often to confine the patient to bed for two or three weeks until the heart has gained sufficient strength under the medication to carry on It is to be recalled, too, that only a fraction of a grain a day may be the optimal dosage

Altogether, few accomplishments in the life of the physician so closely approximate the miraculous as does the rapid im provement of a patient properly treated for thyroid deficiency The body is freed of its impeding load of inert tissue materials and cell nutrition picks up throughout The sense of physical and mental inadequacy gives way to a feeling of well being Work that had previously led to dispiriting fatigue becomes a joy Facial dullness is superseded by animation The friends and family rejoice in the marked improvement in the disposi tion Mental keenness is restored Most gratifying of all, per haps, is the result when a sluggish, dull witted child is placed on the way to normal development To achieve satisfactory re sults, however, the treatment should begin early After a few years' delay, the only outcome may be the conversion of a harmless, apathetic idiot into a mischievous, truculent, trouble making semi idiot (Simpson)

Colloid Goiter

As previously noted, the first thyroid disease to have been recognized was "goiter" Although the term may include other

technical varieties, it usually means *non-toxic* or colloid goiter Because of its tendency to appear at puberty it is often known, too, as *adolescent* goiter Since it occurs in many people in certain regions of the world, the term *endemic* goiter is also applied to it

Endemic *goiter belts* are found in many parts of the world, notably in the Swiss Alps and in the neighboring regions of Italy, Germany, and France The disease is common in some parts of the Balkan Peninsula and in restricted areas in Sweden, Norway, Finland, and Spain It is frequently seen in certain parts of England—particularly Derbyshire, where it is known as "Derbyshire neck" It is quite prevalent near the Himalaya mountains in India Other centers have been reported in Abyssinia, the Azores, South America, Mexico, and Madagascar In the United States it is most prevalent in the territory around the Great Lakes and in the upper Mississippi Valley, but many cases are noted also in the Pacific Northwest and in restricted localities in Virginia, West Virginia, Pennsylvania, and Missouri It is prevalent, too, in certain French Canadian villages

Just why colloid goiter should be of frequent occurrence in some regions and not in others presents an interesting problem One characteristic common to many of these regions is deficiency of iodine in the soil, hence in the local vegetable foods and drinking water There is no doubt, therefore, that one factor in causing the disorder is simply lack of iodine Some observers emphasize the fact that in many goiter regions excessive *lime* occurs in the water and this, too, may be an important factor McCarrison, working in India, has made observations which suggest that some sort of *infection* also plays a role The success that has been reported in some cases in the treatment of goiter by intestinal antiseptics suggests that the infective agent may be harbored in the digestive tract In one variety of goiter occurring in South America, namely, *Chagas's disease,* the cause is known to be an invading organism, *Trypanosoma cruzi*

Webster has made the remarkable observation that cabbage in the diet of rabbits may cause large goiters Whether this effect is due to some deleterious material in the cabbage or to some missing constituent that results in an unbalanced diet when it is fed is not precisely known The drug methyl cyanide has been observed also to produce goiters, hence the sugges tion has been made that cabbage contains a substance of similar action that interferes with the metabolic processes in the body and that the thyroid becomes overstimulated to compensate for the interference There is no evidence that the consumption of cabbage has any significant tendency to increase goiter in human beings, but Boothby emphasizes the theoretical sig nificance of the experimental evidence as suggesting the di rection which research should take in quest of further knowl edge about the human disorder

The burden of the evidence is to indicate that of these vari ous factors the chief is lack of iodine—an essential raw material for the production of thyroxine The gland, according to this conception, makes an oversupply of secretion to compensate for the poor quality of the product It is the storage of this over supply which leads to the enlargement of the gland

Although no age is entirely immune, colloid goiter or dinarily takes *onset* between the ages of ten and seventeen It tends to recede, even without treatment, as adult life is reached Hertzler believes, however, that a thyroid which has once been goitrous never becomes entirely normal again and that it is always a danger to its possessor because of liability to a degenerative condition in which it produces toxic secretion

The *size* of the goiter varies within wide limits from a slight swelling barely detectable to the touch of a skilled physician to a disfiguring mass weighing several pounds In some back ward regions of the world goiters hanging as a pendulous mass reaching to the waist may be seen The goiter has a tendency to enlarge periodically a few days before each menstrual period or during pregnancy in women and after unusual stress in men

The *symptoms* of colloid goiter vary widely, depending in

part upon the degree of accompanying functional deficiency and in part upon the size and direction of the overgrowth From a cosmetic point of view, the disfigurement varies with the size and shape of the goiter, but the popular taste in a given community influences judgment on this point In regions of Switzerland where the disorder is common it is said that the resulting fullness of the neck is regarded as pleasing Aesthetics aside, mechanical *pressure* has also to be considered Small goiters ordinarily make no difference in this latter regard because the tissues of the neck are elastic and permit considerable degrees of bulging without harm But occasionally the enlargement extends downward and invades the chest cavity In that case breathing may be interfered with and sufficient pressure may be exerted upon the blood vessels and the nerves to cause annoying, or even serious, disturbances Sometimes the goiter grows around the trachea, producing compression that may interfere with breathing Hoarseness and coughing as well as ultimate chronic congestion of the breathing apparatus may result In other cases the nerves which control breathing may be sufficiently affected by the pressure as to give rise to sudden intense difficulty in respiration that resembles an attack of asthma Sometimes the patient is entirely free of pressure difficulties except when lying recumbent, but in that posture episodes of suffocation may appear, even sufficient to arouse him from a sound sleep Some of the other rare pressure effects are dusky congestion of the face and neck, inequality of the size of the pupils, localized spots of pallor or flushing of the face, increased sweating on the face or neck, spasm of neck muscles, pain toward the back of the neck, ringing of the ears, and difficulty in swallowing A rather bizarre type is the so-called "diving goiter" It is typically about the size of a plum and is characterized by great mobility Ordinarily it stays in its proper site up in the neck, but is likely, upon deep inspiration, suddenly to disappear into the chest Severe difficulty in breathing may then be experienced and the

goiter held imprisoned by the excessive effort Suffocation and even death have been thus produced

Despite these manifold possibilities of trouble, the possessors of colloid goiter ordinarily enjoy good health In such instances it may be assumed that an adequate compensation for the gland defect is achieved In that case the goiter is a detriment only cosmetically and through its liability to undergo change to the dangerous toxic type In any event, however, it cuts down the margin of safety should conditions elsewhere in the body set up a need for more hormone Particularly, the state of pregnancy makes such demands and mothers having this disorder are likely to give birth to defective children Similarly, the offspring of animals in the goiter belts are often defective—even fatally so—at birth The prevalence of infantile myxedema in these regions was previously mentioned

In the minority of cases the goitrous patient shows the symptoms of ordinary *thyroid deficiency*, though usually in a mild form The basal metabolic rate is 15 or 20 per cent below normal and fatigability and lethargy—both physical and mental—are complained of The patient tends to put on fat easily The skin and hair are somewhat dry and the nails are brittle In girls, menstruation tends to appear early and the flow to be profuse and prolonged

The *treatment* of colloid goiter, if begun early, is ordinarily simple All that is necessary is to increase the supply of iodine Sometimes this can be accomplished to a sufficient extent by increasing the amount of sea food in the diet The consumption of vegetables grown in districts where the soil is rich in iodine may also be effectual Actually, both methods are a rather troublesome means to a simple end The administration of an iodine salt is generally the method of choice Commonly, sodium or potassium iodide is used In pioneer days rubbing tincture of iodine on the skin of the neck over the goiter was highly regarded, but this amounted to no more than a conspicuous way of introducing that element into the

system—the middle of the back would have served quite as well After the goiter has become well established, the use of iodine is often not efficacious in normalizing function, the gland being no longer able to produce an adequate supply of hormone In that case, the preformed active substance should be supplied Sometimes thyroid tablets by mouth suffice, but intravenous injections of thyroxine may be required

Except for cosmetic reasons, *surgical removal* of simple colloid goiter is, according to most authorities, not indicated The operation is regarded as serving merely to convert a rela tive thyroid deficiency into an absolute one

In case of colloid goiters, as in many other situations in life, an ounce of *prevention* is worth a pound of cure In the young, the disorder is readily forestalled by taking a few grains of iodine salt a year Probably no other preventive measure in the whole field of medicine leads to such happy results with so slight an expenditure of forethought The safety and effectiveness of this prophylactic measure have been amply demon strated in many localities The experience of the City of De troit may be cited as an illustration A survey among the school children, in 1924, disclosed goiters in 36 per cent Public interest became aroused and arrangements were made for the addition of a minute portion of iodine to the table salt sold in the district Within two years the incidence of goiter was re duced by three fourths, and a resurvey at the end of seven years disclosed only $2\frac{1}{10}$ per cent as compared with the earlier 36 per cent Not only was the prevalence of colloid goiter thus greatly reduced, but the number of cases of thyrotoxicosis also fell off For example, in one hospital in 1926 there were one hundred and seventy-six patients treated for this condition but in 1930 only one hundred and fourteen Similar results have been obtained in many other communities—especially Switzerland Summarizing the results of the Detroit work, Kimball wrote, "By the prevention of endemic goiter, Michi gan has eliminated from her schools in the future thousands

Large colloid goiter in a middle aged woman From Blumer's Bed side Diagnosis, *courtesy of Dr Hans Lisser and the W B Saunders C*

A case of postoperative myxedema Basal metabolic rate—20 per cent Courtesy of Dr Robert C Moehlig

A case of exophthalmic goiter Courtesy of Dr Robert C Moehlig

Exophthalmic goiter in a girl of five The chief complaints were of nervousness and bulging of the eyes She also had a rapid pulse and was somewhat underweight The thyroid was moderately enlarged This is a condition that is relatively common in adult but rare in children Courtesy of Dr Allan W Rowe Case reported in Endocrinology 12 737 1928

of cases of feeble mindedness which have in the past and would in the future result from endemic goiter"

In some regions in which goiter is endemic, it is legally obligatory to add iodide to all table salt that is sold It should be obligatory in all A more troublesome method is to supply iodine tablets to be taken especially by children and expectant mothers An adequate dosage is one that averages about one tenth of a milligram a day, though much more is harmless—as is seen in the copious use of potassium iodide in the treatment of other diseases

Hyperthyroidism

Hyperthyroidism in man is a fairly common disorder It may result from either overenthusiastic thyroid medication or overactivity of the individual's own thyroid gland The outstanding *manifestations* of hyperthyroidism are increased nervous tension, accelerated pulse, loss of body weight, and increased oxygen consumption In short, the body tissues are overstimulated throughout The results in the life processes are comparable with those of opening the drafts of a furnace The basal metabolic rate that mirrors this forced draft may be doubled The skin flushes easily, with subjective sensations of undue warmth, perspiration is excessive, as are other secretions Insomnia and tremors of the muscles are other evidences of inner tension Both the sympathetic and parasympathetic components of the nervous system are oversensitive, but the sympathetic usually more so The widespread stimulation of the metabolic processes is evident in the increased output of nitrogenous and other wastes in the urine Calcium is also excreted in augmented degree, leading to depletion of this element in the bones The increased tissue activity is, in a measure, compensated by increased food consumption, but, even so, the supply commonly fails to meet the demand and loss of weight ensues The stored fat of the body is used up, thus increasing the weight loss

When overactivity of the thyroid reaches a pathological degree in man, we have the clinical disease *exophthalmic goiter*, or *thyrotoxicosis* (Graves' disease, Basedow's disease) The cause of the overactivity is still problematic It is produced by some unknown stimulus acting on the gland and possibly similar to, but probably not identical with, a stimulating hormone from the pituitary gland The disorder may take onset at any period from early childhood to old age, but is characteristically a disease of adulthood It is about eight times as prevalent in women as in men In the opinion of some clinicians, exophthalmic goiter represents not merely increased hormone production but also a chemical perversion of the normal secretion That is to say, the hormone is not only excessive in quantity but is abnormal also in quality Those holding this view, however, recognize the existence of true pathological hyperthyroidism, technically known as "toxic goiter" (*thyroid adenoma*) Certain rather vague differences in the symptomatology—and especially in the nervous symptoms—of the two conditions are claimed, but for purposes of this discussion they may be treated together

The disease is commonly accompanied by enlargement of the thyroid gland but may be due merely to intense overactivity (hyperplasia) without increase in gross size The heart is overstimulated, hence the pulse is rapid and strong One of the chief dangers of the disease is ultimate injury of the heart muscles, both from overwork and from the excessive amount of hormone acting as a true poison The breathing is shallow and rapid, the blood pressure is elevated, the patient is often conscious of throbbing of the superficial blood vessels and of those in the goiter itself, the latter disturbance being detectable with a stethoscope as a bruit The basal metabolic rate is high The eyes are pushed forward in their sockets (exophthalmos) and the lids held wide apart, giving rise to a characteristic startled expression

As the disorder progresses, restlessness, nervousness, and psychical excitement become increasingly marked This may

develop into an *anxiety neurosis* so typical as to distract the physician's attention from its thyroid origin The manifestations, in addition to general anxiousness, include labile pulse and palpitation, sweating, muscular tremors, abnormal skin sensations, ringing of the ears, weakness, feelings of heat and cold, and capricious appetite The condition may go on even to the point of a major psychosis

Bleuler describes the *hyperthyroid psychosis* as a chronic condition marked by extreme excitement, dissociation of thought, confusion, delusions, hallucinations of hearing and sight, and eventually of the other senses—taste, smell, and physical sensations In some cases this psychosis in its earlier stages cannot be distinguished from schizophrenia It is finally differentiated, however, by the fact that emotional dullness does not supervene and the stream of thought is less disconnected

In any severe case of thyrotoxicosis, *crises* may arise These are marked by elevation of temperature, agitated mania, and profuse diarrhea Such crises are always dangerous and are likely to result fatally

The *diagnosis* of thyrotoxicosis is made largely from the clinical picture There are, however, other causes for each of the individual features, hence, in doubtful cases, these causes must be eliminated Chief reliance is placed upon metabolic rate determinations and tests of the ameliorating influence of iodine This element is of no help except when the trouble lies in the thyroid Recently, determinations of the concentration of iodine in the blood have also been increasingly advocated for diagnosis

The *treatment* of thyrotoxicosis consists primarily in decreasing the amount of the hormone with which the body is afflicted How this is best to be accomplished has been debated among physicians for many years Some therapeutists believe that the overactivity of the gland is but one manifestation of a constitutional involvement and that the disease is usually best treated by prolonged physical, mental, and emotional rest The

preponderant medical opinion is that surgical measures are the most effective as they are certainly the most expeditious The surgeon makes an educated guess as to how much of the gland should be removed to cut the secretion down to the optimal amount but to leave enough tissue to forestall hypothyroidism A minority of practitioners believe that subjecting the thyroid to destructive doses of X rays or radium is the method of choice In any case, early diagnosis is important to permit treatment before damage to the heart or other structures results

In view of the fact that *iodine* is an effective remedy for thyroid deficiency, it seems paradoxical that it is likewise very useful in the treatment of hyperthyroidism This fact came to medical attention as early as 1867 when Trousseau inadvertently prescribed for a patient tincture of iodine instead of tincture of digitalis, but only of recent years has the drug come into general use It is usually given in the form of Lugol's solution It is of some benefit in toxic adenoma, but much more so in the exophthalmic type The treatment permits the benefit of surgery in many cases that would otherwise be regarded as too severe for operation It has greatly reduced the number of surgical deaths Even in cases that have progressed too far for surgery iodine gives welcome symptomatic relief Despite much theorizing, we are still in the dark as to how the same agent can be effective in both hypothyroidism and thyrotoxicosis Perhaps as good a guess as any is that when iodine is supplied in augmented amount to an overworking thyroid its job becomes so easy that it is able to desist, at least temporarily, from its excessive labors That guess encounters the difficult fact, however, that the overfree use of iodine, as emphasized by German students of the disorder, may lead in itself to hyperthyroidism The paradox suggests that important fundamental knowledge of thyroid physiology remains to be discovered

The claim has been made—but without convincing evidence of its validity—that a moderate degree of overactivity of the thyroid is a lifetime characteristic of some individuals They are described as alert and energetic, with facile emotionality

and well marked initiative "People of thyroid personality [according to one account] are

> characterized usually by a lean body or a tendency rapidly to become thin under stress They have clean-cut features and thick hair, often wavy or curly, thick, long eyebrows, large, frank, brilliant, keen eyes, regular and well-developed teeth and mouth Sexually they are well differentiated and susceptible Noticeable emotivity, a rapidity of perception and volition, impulsiveness, and a tendency to explosive crises of expression are the distinctive psychic traits A restless, inexhaustible energy makes them perpetual doers and workers, who get up early in the morning, flit about all day, retire late, and frequently suffer from insomnia, planning in bed what they are to do next day

That people of this personality type exist is true, but that they owe their exuberant living to generosity of thyroid secretion is more than doubtful It is the common experience of clinical investigators that artificial augmentation of the thyroid hormone by gland feeding beyond the physiological need gives rise to no such enrichment of the personality, but merely to a certain amount of *ill* natured restlessness *In* passing, it may be remarked that none of the other glandular personality types that are glibly referred to in some of the impressionistic literature are any more substantially validated

THYROID AS A DRUG

In view of its marked effect on the chemical processes of the body, it might be supposed that thyroid material would have frequent use as a general "tonic," in addition to its utility in the treatment of hypothyroidism It has not, however, come into any great favor for this purpose Apparently, when the thyroid is supplying its hormone in normal amounts additional quantities have relatively little influence If pushed to the point of accomplishing anything, they have a tendency to cause nervousness, insomnia, rapid pulse, and breathlessness Meyer,

however, has recently reported evidence that the general metabolic and heart stimulating actions of thyroid derivatives can be separated, and it is possible that the metabolism raising fraction might prove to be usable in significant dosage without causing circulatory derangement

The chief nonspecific use that is made of thyroid medication is in the treatment of obesity In the opinion of some specialists, it can profitably be used as a supplement to dieting even when no thyroid deficiency in the case can be detected, but others hold a contrary opinion

On empirical grounds, many endocrinologists give thyroid material along with other gland products in order to enhance their therapeutic effects No satisfactory rationale of the procedure is known, but it often does seem to be effective Possibly something akin to the influence of thyroxine on the "specific dynamic action" of foodstuffs is involved

In the practical use of thyroid substance as a medicament it should, in effect, be regarded as two different drugs In the lower dosage range it often has a building up (anabolic) effect, whereas in the higher range it has the stimulating (catabolic) effect for which it is more commonly prescribed Correspondingly, it may have either a sedative or an exciting influence, depending upon dosage

The dosage varies widely from patient to patient, depending upon several conditions The most important of these is the tissue need When the patient's own gland is contributing a substantial quota of thyroxine the reaction threshold is relatively high, but when the tissues are starving for it they seize avidly upon any that is offered and react in exaggerated fashion The optimal dosage varies with age, and especially in accordance with physiological epochs Starting in infancy, the amount should be gradually increased to a plateau level to extend through childhood With the onset of puberty, larger doses are needed, then a smaller amount through adulthood In pregnancy, larger doses are again required The need for thyroxine—hence the proper dosage—changes with the season,

more being required during the winter and less in summer In actual practice it is wise occasionally to suspend treatment for awhile and then redetermine the optimal dosage

Altogether, the correct amount for any given patient at any given time is that amount upon which he thrives and feels best This may vary from a fraction of a grain to several grains of gland substance a day In making orienting first trials, sight should not be lost of the fact that the effect of a single dose continues to build up for two or three days and then gradually tails off over a period of two or three weeks The effect of repeated doses is thus cumulative

As a final item of orientation, it may be stated that in the case of people who have had their thyroid glands removed in the treatment of heart failure, and whose tissues have not degenerated because of prolonged lack of thyroxine, as little as one tenth of a grain of desiccated thyroid a day often suffices for maintenance Seldom is more than a fourth of a grain needed

In view of the antagonistic effect of the thyroid hormone on the action of vitamin A, it would seem desirable to give supplementary doses of this hormone when thyroid is used as a medicament

CONTROL OF THYROID SECRETION

The thyroid gland receives a rather rich nerve supply but, according to Fulton, none of the fibers reaches the secreting cells, hence presumably their influence is merely upon the circulation of the glands That the nervous system does in some way influence the function of the thyroid, however, is indicated by the propensity of emotional stress to set up hyperthyroidism and by the tendency to revert to a normal functional level when mental and physical repose is secured Sometimes the difficult experimental feat is successfully accomplished of grafting into the cervical sympathetic nerve trunk that supplies the thyroid one of the phrenic nerves that normally bring about breathing movements In that case, each respiratory effort results in a bombardment of the target organ with nerve im

pulses The result is a condition which rather closely resembles hyperthyroidism as seen in man The experiment is not crucial to the question at issue, however, because the effective impulses may go to the pituitary gland which, in turn, sends a stimulating substance to the thyroid, as noted below In any case, nervous influences are not indispensable, as is evident from the fact that thyroid grafts without any nerve supply can keep the individual in good health

Whatever may be the importance of nervous control, the thyroid is subject also to hormonal regulation One of the certain results of destroying the anterior lobe of the pituitary gland is atrophy of the thyroid The reduction of the basal metabolic rate, following the operation, is ascribable largely to the deficiency in thyroxine production that is thus brought about The thyroid atrophy can be corrected either by pituitary grafts or by injecting appropriate extracts The active ingredient in such extracts is known as *thyrotropin* It has been separated in a highly active form as a protein fraction By the use of pituitary extracts, and presumably of purified thyrotropin, a condition can be set up in guinea pigs that closely resembles exophthalmic goiter in man The basal metabolic rate increases sharply and may reach 60 per cent above normal The reaction persists about a month and then gradually disappears, even though the treatment is continued The disappearance can be hastened by giving the animal iodine Microscopical examination shows that during the height of the reaction the thyroid cells are in a state of marked hyperplasia, as they are in the human disease Whether overproduction of thyrotropin is an important cause of human thyrotoxicosis is not known

It is obvious that clinical thyroid deficiency might arise from either destruction of the primary gland or, secondarily, from lack of thryotropin By the same token, hypothyroidism might be treated by the administration of the pituitary product Usually, however, thyroid tablets are preferred as less expensive and less troublesome in that they can be taken by mouth whereas the extract has to be given by injections

The fact that changes in the level of circulating thyroxine bring about alterations in the metabolic proresses suggests a third possibility of control The metabolic changes are reflected in the composition of the blood The composition varies also in accordance with the digestive activities and, especially, with the nature of the food Should the thyroid cells be attuned to respond directly to the various circulating metabolites, nice adaptive adjustments might thus be reached As a matter of fact, whether nature has profited by this possibility is quite un known

In some of the lower forms, Gudernatsch has shown that thyroid secretion and thyroxine release are separately con trolled Whether the same is true in the higher animals is not known

BIOLOGY OF THE THYROID

Despite the fact that the thyroid gland may wreak devasta tion in the life of the individual, either by inefficiency or by overactivity, its real function is not, of course, to create trouble but to promote effective living Not only does it influence the individual body cells directly but it plays a large part in main taining the internal milieu of the body as a whole, a milieu in which the cells can carry out their functions in a normal way As Cannon has emphasized in his book *The Wisdom of the Body*, it is only by the use of an intricate multiplicity of regu lating mechanisms that the internal milieu is kept sufficiently constant to permit us even to exist in the kaleidoscopic environ ment in which our lives are cast Of these mechanisms the thyroid is undoubtedly one of the most important

The part played by the thyroid hormone in the intimate economy of the body cells remains largely unknown, but there is clear evidence that shifts in the thyroxine level are accom panied by changes in functions of the liver, the pancreas, the pituitary and the adrenal glands These structures are all con cerned in the regulation of carbohydrate metabolism, hence it appears that the cells throughout the body are dependent for

their sugar supply, at least indirectly, upon the thyroid secretion Since most of our energy for physical and mental work is derived from carbohydrate, the importance of this relationship is evident Less is known about the control of fat and protein metabolism, but the gross pictures resulting from abnormal thyroid functions suggest that the utilization of these food elements, too, is importantly influenced by this gland From the demonstrated depressing effect of thyroid deficiency on the kidneys and sweat glands, it appears that thyroxine plays an important role in keeping the body freed of waste products Similar reasoning leads to the conclusion that the nervous impulses and various accessory influences determining body-cell functions are dependent upon a normal supply of thyroxine That this hormone has significant relationships to vitamin control—and, especially, the functioning of vitamin A—there is some evidence The immunity processes of the body also seem to be dependent somewhat upon this same secretion

At first thought, the thyroid might appear to be a superfluous mechanism not worth the potential trouble it may cause The lower forms of animals have no such gland, yet may live rather efficiently without it The tadpole, deprived of its thyroid, can carry on and even a human being in a similar strait can maintain a vegetative sort of existence In principle, then, it is evident that body functions can proceed without the thyroid catalyzer In the course of our ancestral history a sufficiently high degree of intrinsic reactivity of the individual body cells to obviate the need of thyroxine could no doubt have evolved Why then, we may ask, has not the body of man and of the higher animals developed to function at its best level without a supplementary accelerator? The answer to the riddle lies no doubt in the fact that we live in an unstable environment A level of activity that is quite suitable for one situation is quite inadequate for another From the known effects of its absence, it appears that the thyroid secretion is one of the chief agencies for regulating the vital speed—one

of our best adaptive mechanisms Without thought on our part, it aids in setting the pace of the body cells from the summer to the winter level—the hibernating animal can readily be awakened by thyroid injections It helps adapt us to changes in diet It aids in mobilizing the energy for epochs of special stress, such as puberty or pregnancy In short, the tides of life are in no small measure regulated by the thyroid gland It will be noted, however, that the instances cited are all examples of slower adaptation Rapid adjustments to environmental changes are brought about by other agents

What part does the thyroid gland play in the slowing down of age? That this structure undergoes atrophy and is converted partly into inert fibrous tissue as senility comes on is sufficiently evident But is this cause or is it effect? Would the taking of thyroid substance in the later years merely overstrain the aging tissues or would it serve to preserve their functional alertness, to forestall their senile regression? The problem demands more systematic study than it has yet had

What part has the thyroid played in evolution? Stockard's theory on that subject was briefly considered in the first chapter of this book Is the Bushman a Bushman because of hereditary thyroid deficiency? Is the restless Nordic such because of hereditary thyroid efficiency? Again the problem is open Riddle's success in creating, by selective mating, high thyroid and low thyroid types of pigeons brings the problem within the realm of research Stockard's breeding experiments with dogs have also led to suggestive knowledge

This much we know We are what we are in no small measure by virtue of our thyroid glands Our development before birth and through infancy depends upon their functional integrity The hurdles of puberty are taken with their aid A pinch too little of thyroxine spells idiocy, a pinch too much spells raving delirium Is it a final beneficent waning of thyroid secretion that permits the untroubled approach of the last long sleep?

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IV. THE PARATHYROID GLANDS

DEATH COMES to most as a kindly sleep But it may come with agonizing muscular cramps These may arise either from certain infections or from destruction of the parathyroid glands Thus, death hangs on a bit of specialized tissue bulking no more in total than a large pea.

So inconspicuous are the parathyroid glands that they were long supposed to be merely detached, insignificant bits of thyroid tissue or small lymphatic glands They were first *described* by Remak in 1855, but credit for their discovery commonly goes to Sandström In 1880, he published a clear description of the glands but regarded them as merely displaced bits of thyroid tissue Their independent functional importance was discovered by Gley in 1891. In the preceding chapter mention was made of the many years of confusion that had existed regarding thyroid physiology, because of the failure to recognize the parathyroids as independent entities

The parathyroids are small, bean shaped, yellowish red organs. Typically they measure about two by four by six millimeters and weigh altogether slightly less than half a gram. In man they commonly occur in pairs, the lower of which are usually larger and may be twice the size of the upper pair. Those of women are larger than those of men Perhaps the most constant characteristic of the glands is their inconstancy They vary widely in size, number, and position In various of the lower animals six or more are commonly found, and even in man as many as twelve in one person have been described.

Typically, they lie by pairs on the inner side and toward the back of each lobe of the thyroid gland The upper pair are found about one third of the distance from the top to the lower tip of the lobes, situated in an impression on the surface of each and separated from it by a thin connective tissue capsule They may, however, be buried within the thyroid substance and, accordingly, are spoken of as the internal parathyroids The lower pair lie about halfway between the equator and the lower tip of the thyroid lobes

In addition to the four typically placed glands, *accessory* or *aberrant parathyroids* may be found in the tissues throughout the neck area from well above the thyroid down into the chest cavity, where they may be imbedded in the thymus gland Under normal conditions these scattered parathyroids are of no particular significance, but when they become sufficiently diseased as to require surgical intervention the search for them may be a tedious procedure

The parathyroid glands receive their main blood supply from the inferior thyroid artery, but alternative or accessory vessels may reach the gland from other sources These latter vessels are usually able to assume the function of supplying blood to the glands after the main vessels are ligatured

The *nerve supply* of the parathyroids is rather scanty and is derived mostly from the cervical sympathetic ganglia The fibers are distributed through plexuses which accompany the entering arteries Inconclusive evidence indicates that the nerves have vasomotor rather than secretory functions

Nothing comparable to parathyroid tissue has been discovered in the invertebrates The glands first appear in the scale of life at the amphibian level and are found in all vertebrates except the fishes

In their *embryological development* the parathyroids, like the thymus, develop in relation to the primitive gullet from the tissues of the primitive gill apparatus Paradoxically, the lower parathyroids take origin from the third gill cleft region, whereas the upper pair arise from the fourth cleft The para

dox is rectified by the upward migration of the lower sprouts and downward migration of the upper ones, along with that of the thymus In the foetus the parathyroid cells are arranged in a loose network It is not until after birth that glands become more solid and differentiated into their final structure The latter is not fully reached until puberty

In *histological structure* each parathyroid gland is a roughly globular body made up of a capsule of fibrous tissue and a mass of epithelial cells separated by bands of connective tissue which are continuous with the capsule The cells are arranged in columns or clumps Quite frequently they are grouped in fairly well-defined follicles somewhat like those of the thyroid gland, a fact which long led to their confusion with the latter Two types of components can be recognized, the *principle* and the *oxyphil* cells, the latter of which have a marked affinity for eosin and similar stains What may be the functional relationship between the two types is not yet known

PARATHYROID DEFICIENCY

Our first knowledge of the functional significance of the parathyroids was obtained by noting the effects of their removal from the body Within a day to a week there follows a condition marked by muscular tremors, then by cramps and convulsions The disorder is known technically as *tetany* The tetany is due to increased excitability—partly of the muscles themselves and partly of the nervous system Each muscular contraction multiplies the stimuli with which the sensitized nervous system is bombarded, and thus a vicious circle is set up

In some cases, however, parathyroid deficiency results not in tetany but in a severe or fatal progressive lethargy associated with malnutrition and early death Cats often, and dogs sometimes, show this reaction Just what determines which reaction shall occur is not well known, but there is some evidence of a geographical factor, in certain regions most subjects show the tetanic reaction, in other regions, the nutritional

Susceptibility to parathyroid deficiency becomes progressively less from youth to old age An elderly animal will withstand the loss of three fourths of his parathyroid tissue without apparent effect, and the symptoms of complete deprivation can be more easily controlled by appropriate treatment than is the case in a younger subject On the other hand, the susceptibility to such deficiency is increased by pregnancy, lactation, muscular exertion, fever, and infections The functional condition of the thyroid gland also seems to be a factor

Just how lack of parathyroid secretion leads to tetany is not entirely understood The symptoms that follow removal of the glands are strongly suggestive of the operation of a *toxin* Thus similar convulsive reactions can be induced by the use of *strychnia* or, indirectly, by the virus of *rabies* (hydrophobia) *Tetanus* (lockjaw) is another convulsive disease due to the action of the toxins produced by the tetanus bacillus That parathyroid tetany is actually due, in part at least, to the action of a toxin or toxins is indicated by several evidences Koch and Paton independently succeeded in isolating from the urine of animals in tetany a definite poisonous substance, *methyl guanidine* It is a compound somewhat similar in chemical structure to one of the normal body constituents, *creatinine*, from which it is derived Injections of methyl guanidine into normal animals cause a striking increase of body irritability, giving a picture that, superficially at least, closely resembles parathyroid tetany Unlike the latter condition, however, it is not relieved by calcium treatment nor by parathyroid extracts, and other technical differences have been noted It would seem, therefore, that while guanidine intoxication plays some part in the genesis of the condition under discussion it is not the sole cause of the disorder Dragstedt has reported observations which indicate that the intoxication of parathyroid deficiency arises, in part, from the alimentary canal Withholding meat from the diet, preventing constipation, and administering copious amounts of fluids may serve to keep an animal in excellent health after the complete removal of the glands Such animals

can even go through a pregnancy without showing intoxication, although, as previously mentioned, that condition ordinarily aggravates the symptoms of parathyroid deficiency—sometimes to the point of causing death

Many observers have been struck with the resemblance between the effects of parathyroid deficiency and those of abnormal alkalinity of the body fluids (*alkalosis*) If one increases the alkaline or, what amounts to the same thing, decreases the acid properties of the fluids by the administration of sodium bicarbonate, convulsive effects are sometimes obtained A similar state of affairs can be induced in susceptible subjects by rapid, deep breathing or by excessive vomiting, both of which result in acid depletion It is doubtful, however, that uncomplicated alkalosis plays any great part in the production of parathyroid tetany, though it might serve to accentuate the disorder Actually, the body fluids are not usually unduly alkaline and in the height of the convulsions they even become almost acid

Apparently the most important factors in the production of parathyroid tetany are a disturbance of *calcium* (lime) metabolism and variations in the calcium phosphorous equilibrium Since the work of MacCallum in 1909, it has been known that removal of the glands causes a marked fall in the calcium content of the blood Conversely, parathyroid convulsions can be quickly checked by the injection of calcium salts If calcium therapy is pushed vigorously, all signs of tetany can be kept in abeyance It thus appears that in our normal blood calcium we all make continuous use of a physiological sedative

Just how the parathyroid secretion operates to maintain calcium equilibrium has presented a difficult problem It acts in part, apparently, by controlling the absorption of this element from the alimentary tract In an animal suffering from parathyroid tetany the symptoms are more amenable to calcium if parathyroid extract is administered at the same time, and the extract alone is less effective than when combined with calcium medication Experiments indicate, too, that excretion of

calcium through the intestinal wall is lessened by such extract, whereas destruction of the glands causes severalfold increase in the output It would seem, then, that the glands function both as conservators and as aides in the acquisition of calcium Actually, the subject of calcium metabolism upon which we are here touching is an intricate chapter in physiology Further discussion would lead into complexities beyond the scope of this book

THE PARATHYROID HORMONE

The foregoing facts, while they suffice to show that the parathyroids have an important influence in regulating the calcium metabolism, fail to prove that they produce an internal secretion The organs might conceivably produce their effects by removing something from the blood rather than adding any thing to it This same ambiguity arises in any case in which deprivation symptoms are used to elucidate endocrine functions Logic requires the additional step of demonstrating a unique potency of extracts of the given gland and the ability of such extracts to correct the deprivation symptoms The characteristics of parathyroid extracts, as now known, strongly support the belief that the glands do produce a true hormone This is known as *parathyrin*

While suggestive results had been reported by several previous observers, attempts to derive consistently potent extracts of parathyroid substance had been so uniformly unsuccessful as almost to have marked the problem as unsolvable Then, in 1923 and 1924, three investigators—Hanson, Berman, and Collip—succeeded independently and almost simultaneously in reaching the goal The essential trick of the process consists of boiling fresh gland substance in a weak solution of acid The difficulty that had long defeated investigators was that, although acid is necessary to liberate the hormone, too much acid or too long boiling destroys it Fairly pure extracts are now available, but the actual hormone itself has not yet been iso-

lated Since the extracts are destroyed by digestion with pepsin, the active principle is probably a proteinlike substance

The most striking effect of parathyroid extract is to cause a marked increase in the calcium content of the blood To produce this result it must be introduced either subcutaneously or into a vein It is not effective when taken by mouth—probably because it is digested before it can be absorbed Following a single injection the blood calcium rises gradually for several hours, remains for a short period at a plateau level, then gradually falls The extent of the rise depends upon the size of the dose Ordinarily, single doses have no ill effect unless the amount injected is very excessive If enough is given to increase by half the quantity of calcium in the blood, vomiting may occur and the blood may show an increased tendency to clotting, but neither result is ordinarily at all serious

If a massive dose is injected, the blood calcium may be doubled in amount and death supervene on the second or third day On the other hand, repeated injections at short intervals, even of relatively small doses, result invariably in the death of experimental animals (dogs) and presumably the same result would be seen in man The blood under such conditions becomes so thick that it can scarcely pass through the capillaries and circulatory failure results Different animals, however, show somewhat different responses to the extract While dogs are highly susceptible, rabbits are almost immune to deleterious effects Associated with the increase of blood calcium is a decrease of blood phosphorus But both calcium and phosphorus are excreted in abnormal amounts, hence if the injections are long continued the body is left depleted of these two highly important elements

If the mineral depletion is long maintained the body begins to draw upon the supplies of calcium and phosphorus that are stored in the bones and their tissues ultimately become structurally disorganized The teeth, for some unknown reason, are spared but the changes in the jawbones often lead to their becoming detached and falling out in an intact condition

CLINICAL DISORDERS OF THE PARATHYROIDS

Hypoparathyroidism—Parathyroid Tetany

Despite the fact that disturbances of the function of the parathyroid glands are capable of producing serious and even fatal disorders, they commonly carry on their work so perfectly throughout life that attention is never directed toward them Thus, in the case of these glands, as in various others, every one lives on a slumbering physiologic volcano with never a thought of his potential danger

Clinical parathyroid deficiency may be seen in two grades, the acute and the subacute The most common cause of the *acute* form is the accidental destruction of an undue amount of parathyroid tissue in the course of an operation upon the thyroid Although goiter operations have been carefully standardized to conserve them, the parathyroids are occasionally situated deep within the thyroid tissue and thus may be unwittingly removed with the latter Another danger in case of glands abnormally situated is the inadvertent interference with their circulation Rarely, dangerous deficiency of parathyroid secretion arises from destructive hemorrhages into the glands or from pathological degeneration, presumably as a result of infection

The results of acute parathyroid deficiency, no matter how caused, are commonly essentially the same They include, as previously indicated, hyperexcitability of the entire nervous system, spasmodic and frequently painful muscular cramps, and, later, convulsions The convulsions are almost always symmetrical on the two sides of the body Various disturbances of nutrition also arise, especially in childhood

The *symptoms* commonly begin within one to two days after the injury of the glands The patient usually first becomes apprehensive and conscious of a peculiar sensation of "quiverings" throughout the body, but these symptoms may be preceded by headache, a feeling of weakness, and radiating pains in the

limbs The first manifestation seen by observers is a peculiar posture of the hands with the fingers grouped together and the thumb drawn across the palm ("obstetrician's hand") The contraction (*contracture*) of the muscles thus manifested tends to spread to the wrists and forearms, the feet, and finally the trunk muscles In the meanwhile, twitchings or actual spasms appear and these are often accompanied by severe pain Should the cramps extend to the muscles of respiration there is always a possibility of fatal asphyxia The immediate cause of the symptoms is an increasing deficiency of the blood calcium At the stage of muscular twitchings the level is found to have dropped from the normal ten milligrams to eight milligrams per cent As the symptoms progress the fall continues, to reach a fatal level at about five milligrams

The classic *treatment* of acute parathyroid deficiency is addressed to the low calcium titer in the blood The most effective immediate resource is to inject a solution of calcium salt by vein, or into a muscle Calcium gluconate may be used in dosage of about four grams in 20 per cent concentration This raises the blood calcium immediately and cuts short the attack But the effect lasts only a few hours In the meanwhile, calcium gluconate by mouth may be started with supplementary use of ultraviolet rays and vitamin D The vitamin has the disadvantage of coming into effect only slowly, but has the advantage that the effect of a single dose lasts for about two weeks

Control of the diet, as Dragstedt first showed in experimental animals, is an important adjunct to the treatment and in the milder cases may suffice without other measures High calcium foods, and especially milk and cheese, are valuable Meat, on the other hand, is deleterious, possibly because of its high phosphorus content Constipation should sedulously be prevented Fluids should be given freely Desiccated thyroid substance is also sometimes administered as an adjunctive measure because of its influence in mobilizing calcium from the bones

Often, in addition to these other measures, parathyroid ex

tract is also used It takes about four hours to produce its effect and the benefit persists for about twenty four hours The dosage that is required varies widely from one patient to another, hence must be determined individually In actual practice the use of parathyroid extract has not been very satisfactory, partly because of its high cost and partly because patients commonly become more and more refractory to the extract the longer it is used For instance, Lisser has reported a case of tetany in which gratifying therapeutic results were obtained in the earlier months but in which the patient finally died because of failure to respond to even enormous doses of extract

Recently, and largely through the work of Albright and his associates, the management of parathyroid deficiency has been materially simplified The studies have been addressed both to diagnosis and to treatment When confronted with a suspected case of the disorder, the diagnostic key is the level of the blood calcium While this is technically somewhat difficult to determine by chemical analysis, it can be gauged with sufficient accuracy for practical clinical purposes merely by a rather crude test of the amount of calcium that is being excreted in the urine This is determined by the addition of Sulkovitch's buffered oxalate solution in standard amount If the urine remains clear, it can confidently be assumed that the calcium of the blood is substantially low—in a range of from five to seven milligrams per cent If a fine white cloud appears, showing a moderate amount of calcium in the urine, that of the blood can be judged to be in the normal range If the sample becomes definitely milky, some degree of excessive calcium in the blood is indicated

Instead of depending upon parathyroid extract, Albright uses a synthetic substitute which has the same effects on the blood calcium as does the natural substance, but which does not give rise to refractoriness The material is known as *dihydrotachysterol* or "AT 10" It is obtained as a by product in the manufacture of artificial vitamin D by the irradiation of cholesterol In actual practice the patient makes his own tests and

modifies the dosage according to results He begins with about three cubic centimeters of standard solution (fifteen milligrams of the drug) a day and takes this until calcium appears in the urine, after which a maintenance dose of about one cubic centimeter three to five times a week serves to keep the calcium in proper balance

It is a fortunate circumstance that in human cases of parathyroid deficiency a certain amount of functional tissue is still present even when severe tetany has developed Accordingly, if the patient can be tided over his emergency the tissue commonly increases in amount and resumes the production of an adequate supply of the hormone Thus ultimate cure results

Partial deficiency of the parathyroid secretion may arise and persist for months or years without giving rise to any of the frank symptoms of acute deficiency Nevertheless, the health may suffer severely The condition is known technically as *latent tetany* (chronic tetany) For the diagnosis of this disorder the physician uses a number of special tests These consist of various methods of demonstrating abnormal irritability of the muscles and nerves The most important sign of latent tetany is *Erb's* phenomenon, which is an excessive and qualitatively abnormal response to stimulation with a galvanic electric current *Chvostek's* test is to tap the facial nerve, if latent tetany exists there results a quick contraction of the muscles supplied by that nerve, and especially those of the nose and lip This test is more reliable in children than in older individuals *Trousseau's* phenomenon, which is a sudden contraction of the fingers and the hand, is produced by pressure upon the arm sufficient to stop the circulation

Although frank spasms usually appear only under special conditions—as the term "latent tetany" implies—the nerves and muscles are in a state of *chronic irritability* There is considerable tendency to stiffness of the joints, movements may be painful and the condition is sometimes mistakenly ascribed to rheumatic arthritis (rheumatism) The muscles of the face may be held rigidly and stiffness of the tongue and throat may

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interfere with speech and with swallowing Episodical contractions of the larynx (stridor) may occur to produce choking and cyanosis and at times even death Disturbances of *nutrition* are seen, the manifestations including baldness, brittleness and grooving of the nails, and horizontal grooves or pits in the teeth Cataracts in the eyes are not uncommon, and are due to alterations of the lens proteins The blood calcium is somewhat reduced, but not as greatly as in acute parathyroid deficiency The nutritional disturbances are due in part, apparently, to direct interference with the cellular activities of the various body tissues and in part to influences exerted on the *digestive system* Shelton has reported, for example, three cases of children in whom the "tone" of the lower intestine was so slack as to cause marked dilatation and consequent severe chronic constipation The condition was treated successfully by injections of parathyroid extract

There is considerable evidence that the parathyroid glands are involved in another disorder of childhood, namely, *rickets* This supposition is supported among other evidences by the fact that experimental rickets in chickens is accompanied by excessive development of the parathyroid glands Since, however, the disease in children yields readily to appropriate treatment with sunlight and vitamin D, the glandular relationship, as a practical matter, commonly does not come into the therapeutic equation

Many clinicians believe that, in addition to true tetany, parathyroid deficiency plays a part in a variety of other disorders that are marked by nervous or muscular irritability Even epilepsy is thought by some to be, in a measure, dependent upon this cause

That parathyroid deficiency may have important influences upon behavior has also been noted McCollum is authority for the statement that "No one with blood containing slightly too low a calcium content and markedly low phosphorus content has a wholesome attitude toward life The accompanying ir

irritability, lack of agreeableness, and lack of serenity must be an important consideration in determining the attitude toward home, school, and associates" Earlier mention was made of the fact that parathyroid deficiency results in depletion of the body's supply of calcium and phosphorus Bearing out McCollum's statement, Shannon has recently reported the cases of eight children who developed convulsions followed by mental depression and irrational speech The condition progressed to acute maniacal excitement with screaming, fighting, and tearing of the clothes Even in sleep the dreams were beset with terrors In six of the cases the condition was relieved by parathyroid extract Timme, too, has reported a type of personality disorder in which the parathyroids seemed to play a role The subjects were so "touchy" as to fly into ungovernable rage upon the slightest provocation—an unfriendly look or a mildly critical comment Under treatment with parathyroid extract supplemented by calcium and sunlight a striking reformation occurred Whether these glands play an everyday role in controlling our mood swings presents an interesting problem The evidence as yet available scarcely permits more than entertaining speculation

Hyperparathyroidism

The only known clinical manifestation of oversecretion of parathyroid hormone is the disorder *generalized osteitis fibrosa cystica*, or *von Recklinghausen's disease* Apparently the first recorded case of this disorder was that of Courtial, which was described in 1700, though without recognition of its cause In 1906, Erdheim cast suspicion upon the parathyroid glands when he drew attention to their enlargement in certain cases of bone disorder, but he regarded the gland enlargement as a secondary manifestation In 1915 Schlaugenhaufer argued that the parathyroids are causally involved in such cases Strong support for this newer view was obtained by Mandl in 1926, when he found

a parathyroid tumor in a patient suffering from osteitis fibrosa cystica, when the tumor was removed considerable improvement resulted

Usually in this disease only one of the four parathyroid glands is affected, but occasionally two are simultaneously involved The usual finding is a definite tumor, an adenoma, but occasionally only hyperplasia is seen Rarely, the four glands may be normal but an aberrant gland may be affected Though the tumor is often very small, it may be as large as a walnut Under the microscope the tumor tissue is seen to resemble that of an ordinary parathyroid gland, being made up of both basophil and oxyphil cells

The disease is more common in men than in women and usually develops in the middle decades It is, fortunately, a rare disorder Its onset is usually gradual with asthenia, bony deformities, spontaneous bone fracture, and muscular or bony pains as the chief symptoms Occasionally, involvement of the kidneys giving colic or uremia stands in the foreground of the picture

All of the *bones* are usually involved, but the spine and the long bones are commonly most affected They become soft with resulting bending and deformity The legs become bowed with increasing difficulty of walking, the gait being awkward and waddling Absorption of the tissue of the vertebrae may lead to buckling of the spine with considerable loss of height Ultimately the patient is compelled to take to bed

X ray photographs of the *skeleton* show that two processes are taking place simultaneously A decrease of density (osteoporosis) throughout the bony tissue indicates depletion of the lime salts Here and there the tissue is completely destroyed with cyst formation, which leads to easy fracturing When fractures occur they are slow in healing Often the destructive process invades the bone marrow, where blood cells are formed, with resulting anemia Along with bone destruction compensatory changes are simultaneously occurring, these being the laying down of fibrous tissue within the cysts and deposits of new,

bonelike tissue in abnormal sites These excrescences occur most often at the ends of the long bones and on the jaw The swellings are often tender

In the *muscles* lack of tonicity is common in contrast to the increased tenseness in the opposite condition of parathyroid deficiency Ultimately, the muscles show considerable atrophy and become painful to touch With the wasting in the muscles excessive mobility in the joints may be seen

The *blood calcium* in von Recklinghausen's disease is nearly always abnormally high, ranging from twelve to twenty milligrams per cent as compared with the normal ten milligrams Ordinarily the blood phosphorus is low, while the blood enzyme, *phosphatase*, which controls phosphorus metabolism, is high—sometimes tenfold the normal amount being found The excessive level of calcium in the blood leads to its deposit in many abnormal sites in the body—among these the walls of the stomach and intestines Perhaps for this reason disorders of the digestive system are common These include failure of appetite and intermittent nausea with consequent loss of weight Abdominal pains and cramps like those of gastric ulcer or appendicitis may occur Constipation is the rule

In the *kidneys* calcium may be deposited either diffusely in minute particles or in larger masses Diffuse deposits give rise to the signs and symptoms of chronic nephritis with polyuria, albuminaria, casts, and high blood pressure The high urine output leads to excessive thirst with consequent polydipsia. Interference with the excretion of nitrogenous waste products may give rise to uremia When the deposits are larger, kidney stones may be formed and these may give rise to agonizing attacks of colic. Of late years it has become recognized that in all cases of renal colic the condition of the parathyroids must be considered (Albright)

Presumably because of the disturbance of calcium metabolism the functions of the *nervous system* become abnormal The most common manifestation is apathy, though nervousness and irritability, and sometimes mental confusion, are seen

The *diagnosis* of the disorder necessitates the consideration of several other bony diseases which more or less resemble the one under discussion Sometimes the differential diagnosis can be reached by recognizing the peculiarities of these individual diseases, but reliance is placed chiefly on studies of the blood chemistry The increased calcium with decreased phosphorus is characteristic and high phosphatase titer is also of some diagnostic significance, though this latter is found in numerous other bony disorders

Unless the disease is suitably treated, it is *invariably progressive* Death commonly results from some intercurrent infection, and especially from pneumonia The only effective treatment is destruction of the redundant parathyroid tissue The use of X rays or radium may be helpful, but is rarely sufficient Surgical intervention is perhaps always indicated as soon as the parathyroids are definitely incriminated The individual glands are successively laid bare until the offending one is detected and removed Should all four glands appear normal, the search is then continued into the neck and the chest cavity in search of abnormally placed tissue If no parathyroid tumor is found, the favored practice is to remove two of the normal appearing glands in the hope of sufficiently diminishing the secretion to arrest the disease

The chief danger of the operation is that in the presence of one overactive gland the remaining parathyroids may have relapsed into secretory inefficiency, so that removal of the abnormal one may leave the patient without an adequate amount of hormone In addition, the exploration of the other glands in search of the culprit may seriously interfere with their circulation, leading also to functional deficiency Should hypoparathyroidism thus arise, it is treated as such with calcium salts, vitamin D, and, if necessary, parathyroid extract or dihydrotachysterol Commonly, if the patient is tided over the acute phase, the remaining parathyroid tissue soon resumes an adequate degree of activity and treatment can be discontinued

The immediate results of the operation are disappearance of

pain in the limbs, increased strength, and dropping out of the gastrointestinal and kidney symptoms The adventitious bony deposits of the jaw and elsewhere disappear within a few weeks Restoration of the bone calcium occurs within a matter of months The existing skeletal deformities are not corrected, but with arrest of the disease process it may become practicable to treat them by secondary operations

CONTROL OF THE PARATHYROIDS

Whether the parathyroid glands are subject to *nervous control* is not known As previously mentioned, their nerve supply is scanty and the fibers are distributed to the blood vessels rather than to the gland cells The fact that parathyroid grafts without nervous connections can function effectively shows that nervous control is at least not necessary to their activity

The case for *hormonal control* is not greatly better, though there is some evidence that the parathyroids may be under the influence of a hormone from the anterior lobe of the pituitary This has been somewhat precociously named *parathyrotropin* When the developing pituitary tissue is removed from tadpoles they are unable to metamorphose into frogs, and among their other structural abnormalities is failure of normal development of the parathyroid glands This failure might—or might not—be due to deprivation of a controlling hormone A few investigators have reported enlargement of the parathyroid glands following the injection of anterior pituitary extract in dogs, but other laboratory animals have not shown the reaction and about one third of the dogs failed to respond There is some evidence that changes in the secretory level of the thyroid gland may influence the parathyroids It is possible that one factor in the control of the glands is merely a local response of the parathyroid cells to changes in the level of circulating calcium The fact that calcium deprivation increases tissue irritability, while excessive calcium is a sedative, renders such a theory fairly plausible Such a regulatory mech

anism might suffice for day to-day adaptation The fact that clinical hyperparathyroidism can persist in the face of pro longed elevation of blood calcium shows, however, that direct calcium control would not be a very potent agency The problem of parathyroid control is in need of further study

BIOLOGY OF THE PARATHYROIDS

These glands have been conclusively shown to have an im portant regulatory influence upon the metabolism of calcium and phosphorus, the elements of which bones and teeth are principally made up In addition, and possibly by virtue of their relationship to calcium metabolism, the glands play an important role in maintaining the nervous system in a state of optimal irritability Similarly, the responsiveness of muscular and perhaps glandular tissue to stimulation is influenced by their hormones

Many studies in comparative biology have demonstrated that the element calcium has a marked influence in determin ing the permeability of the walls of living cells To what extent the various phenomena associated with parathyroid disturbances are due simply to changes in cell permeability is, as a matter of fact, quite unknown Whether the production of toxic materials that has been demonstrated in parathyroid de ficiency is directly related to disturbance of calcium metabolism we are likewise uninformed In any case, some sort of profound alteration of body chemistry is evident

It is certain that we have in the parathyroids, as in the thy roid gland, a potential source of grave, or even fatal, ill health What is the gain that compensates for the danger? On the principle of "the survival of the fit," it may safely be as sumed that an organ with active function occurring in so many kinds of animals is in some way useful to its possessor

The chemist will recognize in the behavior of the parathy roid hormone the earmarks of a *catalyst* As is well known, catalysts do not initiate chemical processes but merely change

the speed with which they are carried out Many processes in the chemical industry are brought within the realms of the practical only by the use of catalysts By their aid a given reaction that might otherwise take hours or even weeks for its completion may be made to occur rapidly

If we seek in the principle of catalysis an explanation of the function of the parathyroid glands we must ask how is life facilitated by the hastening or slowing of processes under parathyroid control? Centering attention upon the element calcium, it is to be noted that accelerated mobilization of this substance is required especially when bony tissue is being rapidly laid down This occurs at two epochs in life namely, in infancy and early childhood and during the growth spurt in the second decade of life During pregnancy, too, there is an extra call upon the maternal organism for calcium for building up the body and particularly the bones of the growing fetus The need of the infant persists and even increases after birth, and this need is met by the secretion of calcium in considerable amounts by the mammary glands of the mother If food calcium is not taken in sufficient amounts, the maternal skeleton is drawn upon

From this point of view, it might be assumed that under the conditions existing in the human body the reactions in which calcium is involved would be too slow without a catalyst to permit development at the most advantageous rate Whether, as a matter of fact, such an animal as the guinea pig, which develops rapidly, has a more efficient complement of parathyroid glands than has the human being, with his notably extended developmental period, seems not to have been investigated Neither is it known whether there is a tide of parathyroid secretion corresponding with the growth epochs

Another topic which invites speculation is the relationship of the parathyroids to cell irritability Under some conditions of life relative lethargy is advantageous Indeed, in some animals this is carried to the point of passing the winter in a state of almost suspended animation known as hibernation Under

other conditions—for example, in the chase or in defense from danger—a high degree of responsiveness, especially in the nervous system, the sense organs, and the muscles, is obviously advantageous Is there a depression of parathyroid function in seasons when the animal in a state of nature has occasion to live at an accelerated tempo? The answer is unknown

If we were informed as to how the parathyroid secretion is controlled, we might deduce something more significant than is now understood as to its *raison d'être* But here again we are confronted with uncertainty

This chapter, then, must close on a note of interrogation The what of the matter is reasonably clear A normal supply of parathyroid hormone is a necessary condition for bodily health The *why* must be left to future research

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V. THE HYPOPHYSIS OR PITUITARY GLAND

EARLY OBSERVATIONS

The existence of the pituitary gland was recognized as early as the time of Galen (200 A D) The name "pituitary," given to it by Vesalius, perpetuates a long held, erroneous theory of its function The term ascribed to the gland the lowly office of secreting a fluid to lubricate the throat (Latin *pituita, mucus*) The secretion was supposed to be poured into the nose by minute channels coursing through the porous cribriform plate of the ethmoid bone That there exist no such passages as the ancients surmised was shown by Conrad Schneider as early as 1660 No other function for the gland being known, it came ultimately to be regarded as merely a vestigial relic.

One of the important functions of the pituitary is the promotion of growth The earliest beginnings of our knowledge of anomalies of that process go back into the legendary past. Giants have been known from time immemorial Many peoples have held the belief that man has descended from races of enormous height Curiously, the legend carried over into modern times through misconceptions of fossil remains Actually, the giants of the neomythology were such huge creatures as the dinosaurs. A picturesque version of the belief is reported in the Book of Deuteronomy "For only Og king of Bashan remained of the remnant of giants, behold, his bedstead was a bedstead of iron nine cubits was the length thereof, and four cubits the breadth of it, after the cubit of a man" This description implies that the king was about eleven feet tall

Goliath of Gath, who suffered through the prowess of the youthful David, is another gigantic figure from the past Pliny mentioned by name an Arabian giant nine and a half feet tall and reported by hearsay two others who had reached ten feet This gradual attenuation brings us to a scientifically verified case, that of Kayanus, a Finn, who was authentically nine feet and two inches tall

Actually, the involvement of the pituitary in bodily over growth was first appreciated in connection with a modified type of gigantism known as *acromegaly* This condition had been recognized as a special type of growth anomaly by Verga in 1864, and he made the further important observation that the pituitary gland in the patient he studied was abnormal The eminent pathologist Klebs, thirty years later, published an excellent monograph on a case of acromegaly He em phasized the fact that the pituitary gland was excessively large, but he was unable to decide whether the enlargement was the cause of, or merely a part of, the patient's general overgrowth To the French neurologist Pierre Marie is usually given the credit for finally determining the relationship of the pituitary to the disease His studies were reported in 1886

ANATOMY OF THE PITUITARY

The pituitary gland, like the adrenal, is composed chiefly of two seemingly independent organs which, in nearly all ani mals, are assembled into one The fact that the chief compo nent parts, the *anterior* and the *posterior lobes*, are brought together and arranged in their final form by a series of rather complex developmental maneuvers offers a hint of purpose fulness in the arrangement, but doubt is cast upon such an assumption by the fact that in the whale the two parts are anatomically independent

From the evolutionary point of view, the hypophysis is a very ancient organ It is found in all classes of vertebrates In the lowest fishes it is represented by an open gland discharg

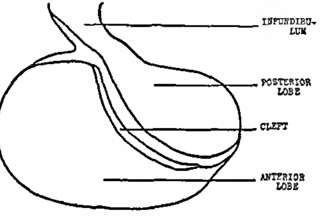
ing its secretion directly into the throat There is a suggestion that in the lower forms it may play an even more important part as a regulator than it does in the higher animals, at any rate, its weight in comparison with that of the brain is greater

In the human *embryo* the first suggestion of the oncoming pituitary is an outgrowth of the mouth cavity, *Rathke's pouch*, that gradually extends toward the brain By the fourth week of life this pouch has made contact with a downgrowth from the brain, the *infundibulum*, and the two parts then develop in association to form the adult gland From the upgrowing pouch, the anterior lobe of the pituitary is fabricated while the infundibular part gives rise to the posterior lobe As will be seen later, the functions of these two parts are as diverse as are their origins

As *development* proceeds, the rear wall of the pouch comes to surround the infundibulum to form the *pars intermedia* (middle portion) of the finished gland The arrangement of the various parts at this time can be roughly visualized by poking a blunt stick into one side of a child's rubber ball to form a double cup The stick represents the infundibulum and the walls of the ball, the anterior lobe material The front portion of the pouch (double cup) grows relatively more rapidly than the remainder and comes partially to surround both the pars intermedia and the posterior lobe To adapt an illustration from Cushing, the finished structure resembles a baseball held in the palm of a boxing glove, the ball being the posterior lobe, the palm, the pars intermedia and the thick back, the anterior lobe The space between the two walls of the early pouch persists throughout life as the *cleft* of the gland Later, the tissues of the posterior or intermediate portion migrate upward along the infundibular stalk which they finally surround like a sleeve, forming the *pars tuberalis* Pituitary tissue extends into the brain as the *median eminence* of the hypothalamus The connection with the mouth cavity is ordinarily lost, the intervening cell mass being absorbed Rarely, a group of these cells persists as an anomaly which may

come to light by their multiplication to form a tumor One remnant, that immediately joining the mouth cavity, usually persists into childhood, or even into adult life, and is believed by some to share in the function of the anterior lobe of the adult gland

By the eighth month of fetal life, in the human species, the blood supply of the pituitary has become rich and secreted



The pituitary of an adult man as disclosed by a cut dividing the gland into right and left halves (Slightly diagrammatic)

material is being deposited in the cleft In the ninth month, even the final cell types are determined How early the gland begins to function in man is not precisely known, but we have some presumptive evidence derived from the study of lower animals From pig embryos about half the length of newborn animals, Smith obtained pituitary extracts that had a growth promoting effect This is the stage, too, at which thyroxine can first be detected in the thyroid gland In amphibia it seems to begin functioning even earlier, as shown by the fact that if the developing pituitary is removed surgically when the tadpole is no more than a fifth of an inch in length, the operation results in fundamental interference with development It is

antecedently probable, from such observations, that the human pituitary begins to function and to play a significant role in fetal development from the early months on

The *adult pituitary* of man is situated almost exactly in the center of the head It is suspended from the underside of the brain like a cherry from a tree The point of attachment lies just behind the crossing of the optic nerve fibers, the chiasm—a fact which accounts for the blindness that sometimes results from pituitary tumors Other important cranial nerves—the third, fourth, fifth, and sixth—also lie in close proximity The gland is well protected in a saddle-shaped recess in the *sphenoid* bone of the skull The recess is known as the *sella turcica* ("Turkish saddle") The four corners of the sella are formed by the *clinoid processes*, these, when seen in profile on the X ray plate, accentuate the saddlelike appearance Pituitary tumors tend to cause erosion of the clinoids, thus giving a characteristic open appearance of the sella as seen on skull plates It is possible, however, for tumor formation to progress quite extensively without such erosion being detectable by X rays The opening of the sella into the skull cavity is shut off by a *diaphragm* of connective tissue The gland is surrounded by a fibrous capsule which, like the diaphragm, represents an extension of the covering of the brain, the dura mater

The size of the pituitary varies somewhat, but in the human adult it is about that of a large pea It weighs from about three fourths of a gram to a gram, or one fifth as much as a five cent piece According to Rasmussen's extensive data, it is larger in tall people, but the gland weight shows no correlation with body weight, as such The glands are larger in women than in men The structure increases somewhat in size with each succeeding pregnancy, a fact which may possibly be correlated with the demands upon the mother for growth material for the developing child In women, a further increase occurs at the climacteric, but in men a similar change is not seen In old age, in both sexes, a slight decrease takes place in the size

of the pituitary with some degree of replacement of the functioning cells by fibrous tissue.

The *blood supply* of the pituitary, and especially of the anterior lobe, is fairly profuse Each internal carotid artery sends a branch to the gland, after supplying minor twigs to the posterior lobe, it pours most of its blood into the sinusoid vessels of the anterior lobe The posterior lobe has, in addition, an independent blood supply from the inferior hypophysial arteries Much interest was aroused at one time by reports that the pituitary is closely connected by its blood supply to the hypothalamic region of the brain, a fact which—if fact—would throw an interesting light on the functional relationship of the two structures It was reported that special venules drain the sinusoids of the anterior lobe, ascend the stalk of the pituitary, and break up into a capillary network within the hypothalamus Because of the resemblance of this arrangement to the portal system of liver drainage, it was designated as the hypophyseo-portal system According to Wislocki's later studies, however, no such arrangement can be found in the higher primates Some, if not all, of the venous blood of the hypophysis drains through the lateral hypophyseal veins and those of the infundibular process directly into the cavernous sinuses

The *innervation* of the pituitary presents a somewhat difficult, but important, problem The anterior lobe can be shown under the microscope to contain nerve fibers which form intercellular plexuses and pericellular networks These have been traced backward to the carotid plexus. Another group of nonmyelinated nerve fibers arise in nuclei, and especially the supraoptic nuclei, in the hypothalamus and pass through the infundibular stalk to the posterior lobe It appears that, in addition to the nerve tracts from the hypothalamus, other fibers are distributed through the superior cervical sympathetic nerves

The pituitary gland is remarkable for the number of active substances, presumably hormones, that can be derived from it Accordingly, many studies have been made of the *histology* (cytology) of the gland in the hope of finding a specific origin

for each of these Under the microscope the tissue of the *anterior lobe* (pars anterior) is seen to consist of solid cords (trabeculae) or nests of cells separated by capillary or sinusoidal blood vessels The cells fall into three types, two of which have marked affinity for dyes and are therefore known as the *chromophile* elements Another group, which do not stain readily, are known as the *chromophobe* cells The chromophobe cells are smaller than the rest and are characterized also by their homogenous cytoplasm In contrast, the chromophile cells are filled with cytoplasmic granules Those which take up acid stains are known as *acidophilic*, while those which have affinity for alkaline dyes are known as *basophilic* Of these various types of cells the chromophobes are the most numerous, the acidophiles next, and the basophiles fewest, but the actual proportions vary widely from one individual to another In his extensive human material, Rasmussen found the chromophobes to average about 52 per cent, the acidophiles, 37 per cent, and the basophiles, 11 per cent

The genetic relationship among the three cell types has afforded an interesting field for cytological research and several theories regarding the matter have been vigorously supported The subject has been intensively studied by Severinghaus His evidence indicates that there are two types of chromophobe cells which are set apart early in the developmental period and serve as mother cells for the more mature types One variety, which is characterized by the presence of *Golgi apparatus*, develops into the basophile cells and the other, which lacks this apparatus, into the eosinophile cells When either type of chromophile cells is actively secreting, the granules may become depleted with consequent reversion to the chromophobe appearance

As previously mentioned, the pituitary enlarges during pregnancy, which enlargement is accompanied by appearance of *pregnancy cells* These are fairly large, actively secreting structures without granulation but rich in *mitochondria* (minute dark-staining bodies), an appearance indicative of high

activity They apparently represent not a new type of cell, but only one which carries out its function without accumulation of granules and hence appears as chromophobic In the late stages of pregnancy, however, there is a significant increase in the number of eosinophilic elements which persist together with some of the pregnancy cells, proper, for months after child birth

Deprivation of the sex organs also gives rise to marked changes in the appearance of the anterior pituitary due to the accumulation of so-called *castration cells* Although variously described by investigators using different staining methods, it appears now that these cells are basophiles which increase in prominence after the operation There seems to be a compen sating decrease in the acidophiles Certain of the enlarged basophiles become vacuolated, the spaces being filled with a colloidlike substance which eventually displaces the cytoplasm and pushes the nucleus to one pole to form *signet ring* cells Although prominent in some species, in others—such as the guinea pig and rabbit—castration cells do not develop As sociated with change in the cytological appearance is a decided increase in functional potency This is evidenced by the ability of anterior lobes of castrated subjects, when grafted into im mature test animals, to bring about enlargement of the sex glands The castration changes of the anterior lobe are re versible and can be prevented by implantation of gonad tis sue or injection of sex hormones The effect of these hormones in this respect is nonspecific, since those of either sex are ef fective in the other There seems, however, to be a sex specific cell pattern which consists of relatively higher eosinophile and lower basophile counts in males than in females This pattern can be reversed by removing the gonads of one sex and re- placing them with those of the other The injection of female sex hormones (estrogens) into normal animals causes loss of granules in both basophilic and eosinophilic cells, but with increase in the number of the basophiles If the injections are sufficiently prolonged, hyperplasia (enlargement) of the an

terior lobe can be produced with eventual formation of small adenomatous (tumorlike) nodules Another cytological evidence of the relationship of the anterior pituitary to sex activity is seen in the accumulation of carmine staining granules at the time of *estrus*, with their rapid disappearance as this period wanes (Dawson and Friedgood)

Changes in endocrine organs other than the gonads can also influence the cell pictures in the anterior pituitary Destroying the *thyroid* gland causes a decrease in the eosinophiles, an increase in the basophiles, and vacuolization of the chromophobe and basophile cells These changes, like those following castration—which they resemble—are reversible, tending to disappear when thyroid substance is administered Giving excessive amounts of thyroid also causes enlargement and vacuolization of the basophile cells, but without changes of the eosinophiles

Destruction of the *adrenals* causes a relative reduction in the number of basophiles Similar changes have been seen in cases of Addison's disease in man, but with considerable variation in details In some instances large chromophobe cells with mixtures of neutral and basophilic granules and of basophiles with lightly staining granules have been seen The latter appearance Severinghaus interprets as representing attempts at compensation

The *growth promoting* function of the anterior pituitary seems definitely to be associated with the acidophilic cells Ordinarily in cases of acromegaly or gigantism, as was shown by Benda in 1900, marked increase in the acidophilic cells is characteristic Commonly this increase is seen in the form of tumors (adenomata), but in rare cases eosinophilic predominance without increase in pituitary size has been reported Thirty years after Benda's report it was shown by Smith and McDowell that anterior pituitaries of a hereditary dwarf strain of mice were completely lacking in acidophilic cells Such animals can be made to grow to the size of ordinary mice by implanting anterior pituitaries from normal strains.

A clear understanding of the cytology of the gland would no doubt contribute greatly to knowledge of pituitary physiology We need to know the precise microscopic appearance that is associated with increases and decreases in each of the pituitary hormones Cytologists, however, have had to contend with certain puzzling facts Apparently when a pituitary cell is completely at rest no granulations at all are produced But excessive activity, in which the granules are used up as rapidly as they are formed, leads to a similar dearth of them On the other hand, the body at a given period may be making very little call upon the pituitary and the gland may be almost at rest but producing more secretion than needed, with resulting slow accumulation of granules Finally, the gland may be vigorously active but keeping somewhat ahead of demand and again with accumulation of granules Thus, paradoxically and confusingly, either presence or absence of granules may indicate either increase or decrease of function Under these various conditions the presence and profuseness of mitochondria may be an important differential indicator of degrees of activity

Much remains to be learned regarding the functional cytology of the anterior pituitary Largely quoting from Severinghaus, the present status of the problem may be summarized Growth abnormalities as seen in acromegaly and in dwarf mice are undoubtedly correlated with changes in the acidophile cells In pregnancy both the acidophiles and basophiles secrete actively, hence are jointly concerned with the changes involved in that state Castration, likewise, affects both cell types, though increase of basophiles seems the more prominent alteration This increase is associated with greater gonad stimulation potency, which indicates that the basophiles are largely concerned in the production of sex hormones There is good evidence, however, that two gonad stimulating hormones are elaborated and it appears that the acidophiles may also be the source of one of these There is additional evidence that both types of cells take part in the hypophyseal control of gonad activity Thyroidectomy and thyroid administration

likewise affect both cell types and the changes in some respects are similar to those seen in disturbances of the gonadal relationship.

So far as is now known, the cytology of other parts of the hypophysis is much less complex than is that of the anterior lobe. The cells of the *pars tuberalis* form a coarse network of cords interspersed with small follicles that are filled with poorly staining colloid material. The individual cells are small, cuboidal in form, and mostly chromophobic, but occasionally a few acidophiles are seen. A rich vascular network permeates the tissue. Atwell emphasizes that the pars tuberalis makes up a larger proportion of the pituitary than is commonly supposed It constitutes 9 per cent of the gland in the cat although a much smaller proportion in man It would seem that enough is present to permit important functioning

The *pars intermedia* of the hypophysis, although derived—like the anterior lobe—from the wall of Rathke's pouch, be comes closely applied to the pars nervosa. A vestige of the pouch cavity frequently remains as the *cleft* of the gland. The pars intermedia varies widely in relative size in different species. In man it is a mere remnant, frequently but a single cell layer in thickness, and even this layer may be interrupted in places It is believed by many observers that at least a part of the active materials that can be extracted from posterior-lobe tissue originates in the cells of this structure. The inter media cells in general are free of specific granules but take a pale basophilic stain. Not infrequently they are ciliated at the ends Certain of the cells, however, are large granular basophiles very similar to those which migrate deeply into the neural lobe. In some animals—for example, rats and monkeys—the pars intermedia consists of large cords of basophilic cells but without very distinct granulation of the cytoplasm In the whale the pars intermedia is lacking. There is fair reason to suppose that the cytology of the intermediate lobe changes with physiological disturbances in the organism, but the evidence is scanty and has not yet been successfully interpreted.

As might be supposed from the fact that it originates as an outgrowth from brain tissue, the *pars nervosa* (neural lobe, posterior lobe) is composed largely of cells and fibers closely similar to those of the central nervous system Prominent among these are angular elements, the *pituicytes*, corresponding to the *neuroglia* cells of the latter Some are definitely granular, others not Nerve fibers from the *supraoptic nucleus* and a more posterior nucleus of the hypophysis enter the pars nervosa through the hypophyseal stalk and either terminate in its substance or continue on into the pars intermedia The *blood supply* is scanty In children often, and in adults occasionally, there are seen projecting into the neural lobe tissue hollow masses of cells filled in many cases with colloid They arise from the hypophyseal cleft in the pars intermedia region The pars nervosa also contains varying numbers of basophiles which, as suggested above, also probably originate in the pars intermedia They are arranged as wedge shaped masses or fingerlike processes, or may be seen as isolated cells There are also present in the pars nervosa colloid-containing cysts of various size made up largely of basophilic cells These latter become more numerous with age An older belief that high blood pressure, or eclampsia, is associated with increased invasions of the basophilic cells is not supported by the exhaustive work of Rasmussen In the rat some cell types have been observed which are not seen in man Prominent among these are large elements containing massive lipoidal droplets These cells vary greatly in number and distribution, they have not been related to any posterior lobe activity Also pigment cells and small rounded chromophobe cells are prominent in this species

EFFECTS OF PITUITARY DEFICIENCY

As is true of the endocrine glands generally, researches on pituitary function have consisted predominantly of studying the effects of induced deficiencies and of the administration of gland extracts The association of pituitary tumors and acro

megaly had been reported many years ago Whether this association represents causality had to be determined by experiment It was foreseen that the studies would necessarily be difficult. Operations on the pituitary require the finest type of surgical skill The gland lies underneath the brain, well protected in the sphenoid bone, where it presents the maximum difficulties of approach The experiment can easily be vitiated either by incidental injury of the brain or by leaving behind fragments of the gland that may suffice to carry on more or less successfully the normal functions of the intact structure

In the earlier years, the erroneous belief was held that the tumors which occur in patients having acromegaly are destructive in nature and, therefore, that the body overgrowth is due to a lack of pituitary secretion Sir Victor Horsley put the assumption to experimental test, attempting to produce acromegaly by destroying the gland He quite failed in the undertaking but the work was of constructive worth because of what was learned regarding experimental technic. The same can be said of several other early surgical studies Sufficient knowledge had accumulated by 1909, however, to permit Cushing in America and Aschner in Europe, independently, to take an important step forward Each succeeded in removing a large portion of the anterior lobe of the gland and keeping his dogs alive The results in brief were that the animals became unusually fat and suffered a regression of both the sexual organs and the thyroid gland Aschner, who worked especially on puppies, emphasized the arrest of growth that ensued The skeleton persisted in the infantile state as did also the sex organs Thus was produced experimentally a condition roughly comparable with naturally occurring dwarfism in man

No attempt was made in these earlier studies to differentiate between the results due to anterior lobe and those due to posterior lobe deficiency The next stage in experimentation was to attempt the still more difficult feat of taking out individual lobes of the gland and leaving intact both the brain and the other lobe What amounted to a fairly clean-cut experi

ment of this nature was a clinical case reported by the Spanish endocrinologist Marañon By accident a boy was shot in the forehead At first no effect beyond that of the wound, as such, could be detected Then there gradually developed a disorder in which marked obesity, genital deficiency, and profuse urine output were prominent features The latter symptom resisted all sorts of treatment except injections of posterior lobe pituitary extract, but by the use of this substance the output was reduced from about two gallons to one quart a day An attempt to remove the bullet resulted in the death of the boy At post mortem examination the bullet was found imbedded in the region of the infundibulum The stalk of the pituitary was contracted by scar tissue that presumably prevented either the production or the distharge of the posterior lobe secretion The anterior lobe of the gland was apparently unharmed As an experiment, this accident was technically defective in that injury to the hypothalamus was not entirely excluded as the cause of the bodily changes that ensued

Perhaps the firmest conviction that grew out of these earlier studies was that the pituitary, and especially its posterior lobe, is intimately related to the processes of water retention in the body It remained, however, for Maddock subsequently to achieve what appeared to be a final clinching experiment to demonstrate the relationship In dogs, pressure was applied to the infundibular stalk by means of a silver clip The procedure resulted in a marked increase in urine output (*polyuria*) It was possible in this experiment to avoid injury to either the anterior lobe or the adjoining brain structures In one case, the polyuria persisted for two years Altogether, the evidence was now rather conclusive that the posterior lobe plays an important part in regulating the water output of the body It appeared, then, that changes in water excretion can in large measure be subtracted from the total picture of pituitary deficiency when one is concerned only with the anterior lobe—as we primarily are in this section of the chapter

In view of the technical difficulties that beset the investiga

tor in the use of higher animals, special importance attaches to experiments that have been made on tadpoles from which the developing pituitary tissue can be removed with relative ease In this form, as shown by the American investigators Smith, Allen, and Atwell, destruction of the gland results in depression of skeletal growth and of failure of development of the reproductive system as well as of two other endocrine organs, the thyroid and the adrenals

All the earlier studies left more or less uncertain the part played by the different lobes in determining the results of injury of the pituitary The matter was then further clarified by the classical researches of Smith, who subjected the whole problem to elaborate restudy, using the rat as the experimental animal One might assume that so small a creature might present insuperable surgical difficulties, but by the aid of a dissecting microscope the problem of reaching and removing the pituitary through an incision in the throat was solved The high resistance of the rat to infection is an advantage compensating for its small size and, furthermore, the pituitary is so shut off from the brain by the tough diaphragm as to render comparatively easy the avoidance of injury of that structure

Smith's first attack on the problem was made, however, not by surgical removal of the gland but by exposing it from one side and injecting into it a destructive substance, chromic acid Rats so treated developed a characteristic set of abnormalities —*dwarfism, adiposity*, and *genital atrophy*—such as previous observers had seen, and, in addition, the thyroid and adrenal atrophy that the tadpole surgeons had earlier produced These experiments had the defect, however, that the spread of the acid through the pituitary stalk into the brain could not be controlled, hence the results were again ambiguous

When, however, Smith turned to surgical procedures, this ambiguity was removed The results of operation differed from those of acid injection in one important respect—obesity appeared, if at all, only months after the gland was destroyed If the operation was performed on immature subjects the

have shown that in tadpoles, at least, the failure of development following pituitary deficiency is to an important extent dependent upon secondary thyroid atrophy Animals lacking a pituitary remain in the tadpole stage indefinitely but can be made to develop into frogs under treatment with thyroid alone or with anterior lobe substance which causes restoration of the thyroid Likewise, the depression of basal metabolism might be ascribed to the secondary thyroid deficiency, but in the rat the degree of lowering after the removal of the thyroid is reported to be less than that which follows destruction of the pituitary Adrenal cortex deficiency, however, also results in a drop in the basal rate and it is possible that the effect of the pituitary deficiency on this function may be accounted for by the joint depression of the thyroid and the adrenals That the genital depression of anterior lobe deficiency is mediated, in part, through the adrenals is shown by Atwell's subsequent work he found that a considerable degree of restoration of genital development can be brought about by the injections of cortin

In summary, then, the results of extirpation experiments and supplementary "replacement therapy" had made clear several important facts regarding the functions of the anterior lobe of the pituitary Deficiency of its hormones results in failure of body growth, failure of sexual development, and depression of the adrenal, thyroid, and sex glands Not only is growth prevented, however, but if the deficiency arises after growth is fairly well along a state of chronic undernutrition may arise Although the animal remains at an infantile (or juvenile) stage of development, the actual life span is shortened The body temperature is lowered as is also the rate of oxygen consumption It appeared that the bodily effects of anterior lobe deficiency are, in large measure, due actually to the associated depression of the functions of the adrenal, the thyroid, and the sex glands But the evidence indicated that the adiposity and disturbed water metabolism that often occur in connection with pituitary deficiency are due ordinarily to de

fects in the posterior lobe or the brain rather than in the anterior lobe

ANTERIOR LOBE EXTRACTS

So voluminous has been the work of recent years on anterior lobe extracts that no brief account can give more than a sketchy idea of it From the fact that anterior lobe deficiency gives rise to a considerable variety of effects it might be surmised that a like number of different hormones are secreted Such an assumption, however, is contrary to the belief of many of the competent workers in the field And this despite the fact that by "chemical dissection," to use Collip's phrase, a very considerable number of active fractions have been derived from such extracts The crux of the matter is that no one has yet succeeded in determining in just what forms the active substances are actually discharged from the gland Even with the utmost care in chemical manipulation the various hormones as secreted may be broken apart or otherwise modified in the test tubes Even complete success in securing chemically pure products with consistently predictable physiological effects would not prove their true hormone status any more than would the securing of pure metal from an ore prove that it had previously existed in that form This is not to gainsay the fact, however, that the obtaining of such purified extracts is highly important both because of their potential value as tools for research and as therapeutic agents

However true it may prove to be, it is believed by some of the most experienced chemists that the anterior pituitary secretes only a few—perhaps two or three—different hormone bodies and that from these, acting singly or in combination, all of the various physiological functions of the gland are carried out Alternatively, it is possible to visualize a large mother molecule containing several active atom groups, each of which can be selectively separated out by the various reacting tissues in accordance with their immediate needs Such groups might

varying from 5 2 to 7 4 and with ammonium sulphate at half saturation or less to precipitate it It has been shown that a purified preparation may cause growth when administered in individual daily doses representing as little as two milligrams (one thirtieth of a grain) of fresh gland substance

In view of the fact that the end result of administering growth extract is a normally developed animal with normal relationships among the parts, it follows that the hormone influences not only the accumulation of body substance but also the differential changes that go with maturity As shown by the work of Mortimer, these are especially evident in the skeleton and the skull The intimate architecture and the blood supply of these are influenced to produce the mature pattern rather than merely enlargement of the infantile structures

The effect of the growth hormone on *body metabolism* has been studied by Lee in hypophysectomized rats He used paired animals in which the appetite of the less voracious determined the daily food quota of both Thus, any influences that might be exercised through mere improvement of the appetite were excluded Evidence was found that the nitrogen metabolism is particularly influenced The growth hormone thus seems to bear a relationship to protein turnover comparable to the influence of insulin on carbohydrate metabolism Although the extract was found to stimulate the appetite, it also brought about more gain in weight in the treated animal than in the control when both ate the same amount of food In two months the excess gain amounted to approximately forty grams per rat At the end of the paired feeding experiments the animals were killed and the bodies analyzed chemically It was found that with the progress of the condition of pituitary deficiency the untreated rats had approached the senile composition pattern The water content had decreased somewhat, the fat content had increased about 50 per cent, and the nitrogen and mineral content had declined in relative proportions

though increasing in absolute amounts The hormone treated animals, on the other hand, were found to have retained on the average one fourth more of the nitrogenous elements of the food than had the controls Their bodies had almost exactly the chemical composition characteristic of the age at which the experiment started

These findings tempt to a generalization that the aging process is especially under the control of the anterior pituitary They justify the conclusion that the growth hormone brings about increased mobilization and more efficient utilization of protein reserves with lessened demand upon the fat stores A similar state of positive nitrogen balance is seen during the normal growth period of children, during the latter part of pregnancy in women, in the course of developing acromegaly, and during the stage of recovery from starvation or wasting diseases Since this positive balance is accompanied by low values in the nonprotein nitrogen of the blood, increase in body weight, and deposition of protein nitrogen—just as in the treated animals—it may plausibly be assumed that the metabolism of all these incremental processes is under growth hormone control

Another important anterior lobe derivative is the *thyrotropic hormone* (thyrotropin) That the pituitary and the thyroid are functionally related was first suggested by Rogowitsch, who in 1888 noted enlargement of the hypophysis after the thyroid glands had been removed from dogs and rabbits A variety of observations in subsequent years confirmed the suggestion Allen (1919) noted, as previously stated, that destruction of the pituitary in tadpoles resulted in an atrophic condition in the thyroid Three years later Smith confirmed the observation and showed that repair of the gland could be brought about either by pituitary transplants or by the injection of anterior lobe extracts He subsequently made similar observations in rats Not only was the architecture of the thyroid normalized but also metamorphosis in tadpoles and increased basal metabolic rates in rats resulted Earlier mention

was made of the work of Loeb and others which showed the possibility of reproducing a condition comparable to clinical hyperthyroidism by giving anterior pituitary extracts to animals

Although thyrotropic extract from one species influences the thyroids of other species, hence presumably is essentially the same in all, the thyrotropic content of the glands of various kinds of animals differs markedly Guinea pig glands give a low yield while those of rats are rich in this hormone Correspondingly, the rat is quite insensitive to it whereas the guinea pig responds to very small doses The thyrotropic content of the hypophysis is influenced by various experimental procedures There is some evidence that it is increased by thyroidectomy and decreased by the administration of thyrotropic hormone—observations which indicate that the body has some sort of mechanism for adjusting supply to demand Castration also lowers the thyrotropic content

Whether thyrotropin exerts its influence directly on the thyroid cells or indirectly through the nervous system has been studied by a number of investigators It appears that grafts without innervation, as well as thyroid cells growing in tissue cultures, are stimulated by the pituitary hormone, hence part of the influence is direct But since the action of the hormone is decreased when either the innervation of the thyroid gland or the hypothalamic region of the brain is destroyed, participation of the nervous system must also be recognized In some species, e g , guinea pigs, the response to thyrotropic hormone is most marked in young animals, and especially females, while older animals are much less sensitive The effects begin very promptly—even within two hours

The anatomical changes in the thyroid depend to a considerable extent upon the amount of thyrotropin injected If extract is given for several days the gland may be increased to three times the normal bulk Under the microscope the acini are found to be reduced in size and largely depleted of colloid The secreting cells are enlarged and have the columnar

shape that is characteristic of vigorous activity The maximal effects are secured when injections are given once daily for a week If continued beyond this period the microscopic evidence of stimulation disappears and the gland gradually takes on the appearance of a resting structure The metabolic effects parallel the local changes in the thyroid Most notable is increase of the basal rate, which may reach as much as 60 per cent The fact that it is due specifically to thyroid stimulation is evidenced by its failure to appear when that gland is first removed The decline in the influence of the hormone with continued use has been ascribed by Collip and Anderson to the production of an antagonistic substance—*antihormone*—in the body of the treated animal Expert opinion is divided as to whether this is the true cause No convincing alternative explanation has been offered beyond the rather vacuous one that the thyroid gland gradually loses its ability to respond Especially because of this waning reactivity with prolonged use, the thyrotropic hormone has so far not proved very useful in the treatment of human patients

The thyrotropic hormone can be extracted from the gland tissue with water or with dilute solutions of either acid or alkali The potency remains after most of the proteins are removed either by ultrafiltration or by the use of precipitating agents such as trichloracetic acid The resulting solution can be further purified by precipitating the hormone with acetone or with methyl alcohol It is soluble in aqueous solutions of ethyl alcohol acetone, and pyridine The active portion can readily be adsorbed from solutions Like the growth hormone which it rather closely resembles, chemically, thyrotropin is also a globulin

We may next consider the *gonadotropic hormones* (gonadotropins) That the anterior pituitary has an important relationship with the gonads is clear As previously stated, destruction of the pituitary in the young causes failure of development of the sex organs and the same operation performed in the

adult period causes a regression in their structure and functions Complementary evidence is the restoration of the sex glands by the use of anterior lobe extracts or by pituitary implants Active material can be obtained from either fresh gland substance or from that dried in acetone It appears in acid, alkaline, aqueous, or alcoholic extracts It does not withstand boiling and its stability decreases with purification

The discussion of the functions of the gonadotropic hormones can advantageously be deferred, for the most part, to subsequent chapters dealing with the sex functions Suffice it in this place to say that despite a vast amount of research the number of different gonadotropic hormones is still problematic At least six effects of pituitary extracts on the sex glands have been noted and each effect has been assigned by one or another investigator to an individual hormone These effects are growth of the follicle of the ovary, maturing of the follicles, secretion of primary ovarian hormone (estrogen), discharge of matured ova from the ovaries, transformation of the granulosa cells of the ovary into lutein cells and similar transformation of the theca cells of the ovary followed by degeneration of the follicles It is probable that only two gonadotropins are actually produced One of these is the follicle-stimulating hormone (FSH) and the other the luteinizing hormone (LH) Clean separation of even these two factors is a rather difficult chemical feat

Although the gonadotropins are named from their effects on the ovaries, they also influence the testes It appears that the FSH acts primarily upon the tissue from which the sperm cells are derived while the LH stimulates the interstitial cells Both products increase the weight of the gonads of males and stimulate descent of the testes into the scrotum when administered to immature rats Regeneration of the accessory male organs—the prostate and the seminal vesicles—is obtainable from LH but not from FSH

The gonadotropic potency of the anterior pituitary varies under different conditions More is obtainable from the glands

of immature females than from those of males The potency is markedly increased by castration, a fact which is interestingly related to the changes in the pituitary cells mentioned in an earlier paragraph The gonadotropic potency is reduced when gonad grafts are implanted or sex hormones are injected The potency is reduced during pregnancy, an effect presumably due to the increased concentration of estrogens in the blood which occurs in that condition It may be this relationship which accounts, too, for the fact that the ovaries during pregnancy cease to discharge ova Deficiency of vitamin E, the "sex vitamin," also depletes the gland of gonadotropin and the same is reported to be true of lack of manganese in the diet There is also considerable variation with species Thus, the pituitaries of sheep give a high yield of gonadotropins and low yield of thyrotropin whereas those of cattle present the reverse condition Pigs' glands give a high yield of both

Potent gonadotropins, similar to or identical with those of the pituitary, are obtainable not only from that gland but also from the placenta, the blood and urine of pregnant women, the urine of women after the climacteric, and the blood and urine of pregnant mares The biological complexity that results from all of these various gonadotropins in action has yielded only slowly to the vast amount of research that has been devoted to the problems Probably, much more remains to be discovered than is yet known The available data will be further considered in subsequent chapters dealing with the sex functions

The probable existence of an *adrenal-cortex regulator* (corticotropin) was suggested by the earlier work of Smith It was shown in rats that marked atrophy of the adrenal cortex followed destruction of the hypophysis and that the degenerative change could be prevented or the normal condition restored by the implantation of fresh pituitaries Early attempts to obtain a pure corticotropic fractioo were impeded by its close chemical similarity to thyrotropin The separation was first made by Collip's group, making use of the facts that thyrotropin is more soluble in alcohol and that it can be precipitated isoelectrically

agency of the adrenal A part of the influence may also be exerted through the brain The effect of anterior lobe extracts is, in general, the opposite of that of insulin, hence the acting agent, whatever it may be, is sometimes referred to as the *anti-insulin factor* In that it aggravates the diabetic condition it is also spoken of as the *diabetogenic hormone* That this hormone exists as a specific entity has been claimed by Anselmino and Hoffman, who report finding it in the blood and urine of diabetic patients These authors state that it increases when carbohydrate food is eaten but that the increase can be prevented by giving large doses of insulin It is supposed that the hormone acts by fixing in some way the carbohydrate stores and interfering with their use by the body tissues Thus, it comes about that when the hormone is eliminated by destroying the hypophysis the body carbohydrate is rapidly oxidized The relationship of the anterior pituitary to carbohydrate metabolism is presumably of much practical importance in the disease, diabetes mellitus, as it appears in man

The relation of the anterior pituitary to *fat metabolism* is important in this same connection One characteristic feature of diabetes mellitus, either human or experimental, is a partial failure of the burning of fatty substances in the body Combustion is halted short of completion and, as a result, partially oxidized acid products accumulate in the tissues and in the blood These substances are known as the *ketones* or *acetone bodies* Several investigators have reported that the injection of a special fraction of anterior lobe extract causes an increase of these acetone bodies The active agent is designated the *ketogenic factor* or the *fat-metabolism hormone* It is said to be discharged from the anterior pituitary in increased amounts when fatty foods are eaten The way in which this factor influences the production of acetone bodies is obscure, but the effect seems to be mediated in part through the thyroid gland All active ketogenic extracts cause an increase in the total fat content of the liver Work in Collip's laboratory indicates that the ketogenic factor is rather stable to heat It can be boiled, for

example, in dilute hydrochloric acid without much loss in activity, a fact which differentiates it from most other anterior-lobe principles.

Collip has reported that there is present in all simple extracts of pituitary tissue a substance which has the property of raising the basal metabolic rate. This he calls the *specific metabolic principle.* The evidence indicates that it acts directly on the body tissues rather than through the agency of any of the glands which especially influence basal metabolism. Particularly to be noted is that it is effective after removal of the thyroid. It is remarkably resistant to heat, being able to withstand boiling even in sulphuric-acid solution. When injected into experimental animals or human subjects, it causes a sharp elevation of the metabolic rate, the effect persisting for several hours. Collip believes that it specifically stimulates the metabolism of fat. It might, therefore, be regarded as an antagonist for the ketogenic factor.

What is known about the *diuretic* hormone of the anterior lobe will be discussed in connection with the antidiuretic hormone of the posterior lobe.

As is evident from even the foregoing meager account, anterior-pituitary substance affords a remarkable variety of fractions which intricately affect the functions of the body. These active principles are mostly, if not all, proteins. Their chemical manipulation is correspondingly difficult. In view of the marked complexity and almost infinite variability of the protein molecule, the hope of producing these substances synthetically is relatively small even after their chemical identification shall have been completed.

Much more remains to be discovered than is yet known regarding the hormone status of the gland. Especially, we need to know to what extent each metabolic activity is represented by a specific hormone or to what extent by combinations of the hormones acting jointly. If, as has been suggested, all of the various activities are carried out through the agency of two or three mother molecules, the nature of these must be deter-

agency of the adrenal A part of the influence may also be exerted through the brain The effect of anterior lobe extracts is, in general, the opposite of that of insulin, hence the acting agent, whatever it may be, is sometimes referred to as the *anti-insulin factor* In that it aggravates the diabetic condition it is also spoken of as the *diabetogenic hormone* That this hormone exists as a specific entity has been claimed by Anselmino and Hoffman, who report finding it in the blood and urine of diabetic patients These authors state that it increases when carbohydrate food is eaten but that the increase can be prevented by giving large doses of insulin It is supposed that the hormone acts by fixing in some way the carbohydrate stores and interfering with their use by the body tissues Thus, it comes about that when the hormone is eliminated by destroying the hypophysis the body carbohydrate is rapidly oxidized The relationship of the anterior pituitary to carbohydrate metabolism is presumably of much practical importance in the disease, diabetes mellitus, as it appears in man

The relation of the anterior pituitary to *fat metabolism* is important in this same connection One characteristic feature of diabetes mellitus, either human or experimental, is a partial failure of the burning of fatty substances in the body Combustion is halted short of completion and, as a result, partially oxidized acid products accumulate in the tissues and in the blood These substances are known as the *ketones* or *acetone bodies* Several investigators have reported that the injection of a special fraction of anterior lobe extract causes an increase of these acetone bodies The active agent is designated the *ketogenic factor* or the *fat-metabolism hormone* It is said to be discharged from the anterior pituitary in increased amounts when fatty foods are eaten The way in which this factor influences the production of acetone bodies is obscure, but the effect seems to be mediated in part through the thyroid gland All active ketogenic extracts cause an increase in the total fat content of the liver Work in Collip's laboratory indicates that the ketogenic factor is rather stable to heat It can be boiled, for

example, in dilute hydrochloric acid without much loss in activity, a fact which differentiates it from most other anterior lobe principles

Collip has reported that there is present in all simple extracts of pituitary tissue a substance which has the property of raising the basal metabolic rate This he calls the *specific metabolic principle* The evidence indicates that it acts directly on the body tissues rather than through the agency of any of the glands which especially influence basal metabolism Particularly to be noted is that it is effective after removal of the thyroid It is remarkably resistant to heat, being able to withstand boiling even in sulphuric acid solution When injected into experimental animals or human subjects, it causes a sharp elevation of the metabolic rate, the effect persisting for several hours Collip believes that it specifically stimulates the metabolism of fat It might, therefore, be regarded as an antagonist for the ketogenic factor

What is known about the *diuretic* hormone of the anterior lobe will be discussed in connection with the antidiuretic hormone of the posterior lobe

As is evident from even the foregoing meager account, anterior pituitary substance affords a remarkable variety of fractions which intricately affect the functions of the body These active principles are mostly, if not all, proteins Their chemical manipulation is correspondingly difficult In view of the marked complexity and almost infinite variability of the protein molecule, the hope of producing these substances synthetically is relatively small even after their chemical identification shall have been completed

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as such or, more commonly, in the unfractionated form, "pituitrin," is to check the flow of urine in cases of diabetes insipidus How the effect is produced is still not certain but it is principally, at any rate, through an influence on the kidneys These organs consist of a complex system of tubular excretory elements Fluid is passed into the tubules through thin walled, dilated end structures, the "glomeruli" Thence it passes down the tubules to be modified in various ways and finally is excreted The best evidence indicates that pitressin diminishes urine flow by causing the tubules to resorb a part of the water previously discharged through the glomeruli It is a remarkable and further complicating fact that this antidiuretic effect is demonstrable only in animals possessing at least some anterior lobe tissue It presumably acts, therefore, by inhibiting the action of an anterior lobe *diuretic* principle Pitressin influences the composition of urine also by increasing the concentration of certain salts, especially sodium chloride

The function of pitressin in the animal economy seems to be to conserve water in conditions when dangerous loss of that substance threatens It is reported that when animals are kept for a considerable period on short water rations this antidiuretic principle is secreted in excessive amounts so that some escapes into the urine It is possible by repeated injections of pitressin to cause such a depression of urine output as to give rise to the serious illness known as "water intoxication" McQuarrie has shown that children liable to epilepsy can be thrown into typical attacks by enforced water retention when pitressin is given Some use has been made of this phenomenon as a clinical test for epilepsy

When excessively large doses of pitressin are given to experimental animals, gastric ulcers and anemia can be produced, but it is doubtful that enough is ever actually secreted to bring about any such effects

The principal clinical use that is made of the *oxytocin* fraction of posterior lobe extracts is to speed up the birth process when uterine contractions are sluggish Of recent years it has

largely superseded ergot for this purpose It must be used with caution, however, because otherwise the contractions become too violent and may even cause rupture of the uterine wall In view of the potency of oxytocin when thus used artificially, the temptation is strong to assume that it plays a normal role in the birth process It has been reported in some animals that the uterus becomes increasingly sensitive to oxytocin in the last stages of pregnancy It might be this increased reactivity that finally induces the onset of labor and promotes it after it is started The evidence, however, does not yet permit final judgment on the point The fact that animals can carry through parturition after removal of the posterior lobe indicates that the mechanism is, at any rate, not indispensable

An interesting characteristic of posterior lobe extract is its influence upon *carbohydrate metabolism* Both fractions seem to be involved, but pitressin rather more so Geiling found that destruction of the posterior lobe sharply increases the sensitiveness of the experimental animal to insulin, the hormone which chiefly regulates the storage and use of carbohydrate in the body Burn has made the complementary observation that the injection of postpituitary extract lessens the effect of a given dose of insulin

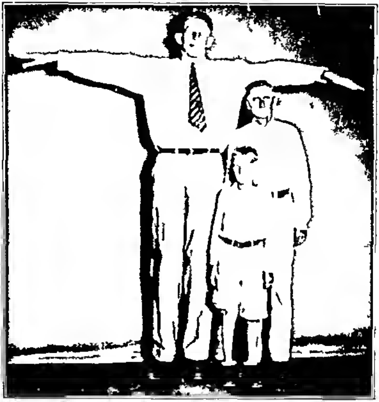
An important relationship of the posterior pituitary to *fat metabolism* has been claimed by Raab He postulates the secretion of a hormone, *lipoitrin*, which is supposed to act on a fat metabolism center in the brain Supporting the theory are the observations that injections of posterior lobe extract cause a reduction in the amount of fat in the blood of both dogs and men, whereas that in the liver is increased This investigator ascribes clinical obesity to lowered sensitivity of the brain center to lipoitrin Further evidence on the subject is needed

In 1938, Neufeldt and Collip reported the separation of an *adrenin antagonist also from posterior lobe extract* It does not vary in parallel with either the pitressin or oxytocin effects, hence it is regarded as being a substance different from either When it is injected together with adrenin, the elevation of

dependent structures, are free of melanophore principle It is now generally believed that it is derived from the intermediate lobe, hence it is often referred to as *intermedin* Essentially all that is known of the functions of the pars intermedia is the foregoing fact Since human beings and other higher animals do not have melanophores, this lobe would seem to be of more interest to zoologists than to physicians That the principle has other functions than control of the pigment cells, however, is suggested by the fact that it is obtainable from the glands of many species of animals which lack melanophores It can be detected in the urine of both men and women and it increases during pregnancy in the latter It has been obtained also from certain pituitary tumors (basophilic adenomas) in man

There is evidence to indicate that the output of intermedin is stimulated by exposure of the animal to light. The reaction of the frog to illumination is abolished either by removing the pituitary or by removing the eyes, hence the light effect is presumably mediated through the optic nerves It has been stated that the concentration of intermedin is higher in the pituitaries of animals with nocturnal habits than in those which remain abroad in the daytime A *raison d'être* for the secretion of intermedin by man and other higher animals is suggested by the fact that it exerts a fairly potent antidiuretic influence As was shown by Sulzberger, when it is administered to patients with diabetes insipidus considerable reduction of urine output and thirst can be obtained However, in this respect it is less potent than pitressin

The foregoing account of the structure and functions of the pituitary gland has been greatly simplified The literature on the subject is voluminous and many interesting observations have been passed over entirely Merely the gist of numerous others has been given and conflicting details from animal to animal and from observer to observer have been largely ignored That the pituitary gland is a highly important one



Photograph of a youth of 1[illegible]½ years, standing beside a 9 year old boy and a man who is 5 feet, 11 inches tall The patient's height was 7 feet, 1 inch, his weight, 2[illegible]8 pounds His hat size was 7 [illegible]8 and his shoes were 1[illegible] inches long, estimated as size 3[illegible] Courtesy of Dr L H Behrens Case reported in Endocrinology 16 1[illegible]0 193[illegible]

blood sugar is materially less than when adrenin is injected alone The biological significance of the material still remains to be determined

The *site of origin* of these various active products of the posterior lobe is still a matter upon which concordance of opinion has not been reached As mentioned in an earlier section, this structure is made up almost entirely of neuroglialike tissue which shows none of the characteristics of secreting cells as seen in the ordinary glands of the body Especially these cells do not undergo the changes of appearance characteristic of cycles of activity in recognized gland cells Thus, while there is no definite proof that they cannot form secretion, it seems improbable that they do so In that case the posterior lobe must be regarded merely as a storage organ for the active principles that are formed elsewhere in the body and brought there by the blood or lymph for storage On that hypothesis, the most plausible source is the anterior lobe and its extensions The storage function seems to be shared, to some extent, by the tissues of the hypothalamic part of the brain which lie near the attachment of the gland

There has been much discussion as to how the active principles of the posterior lobe are conveyed to the rest of the body In the earlier period it was rather confidently believed that they pass up through the infundibular stalk to be discharged into the cerebral spinal fluid Cushing's observation that pituitary extract is more effective when introduced into the hypothalamic area than when injected by vein suggested that when the active principles reached the brain they exerted their effect principally on local centers there The better and more recent work, however, has raised substantial doubt whether discharge through the infundibulum actually does occur The weight of the evidence is that these principles, like hormones generally, are discharged directly from the producing gland into the blood stream

In *summary*, then, it appears that the posterior lobe of the pituitary is probably a true organ of internal secretion Judg

ing by the effects of its extracts, it has important functions in controlling water metabolism and the activity of smooth muscle throughout the body. This latter relationship seems to be of special significance in the case of the uterus, the posterior pituitary may aid substantially in the activities of childbirth, although parturition in animals can take place after destruction of that structure. It seems also to have significant, though as yet vaguely defined, influences upon fat and carbohydrate metabolism. The mechanisms involved here may be antagonism to insulin and to adrenin. There is some evidence that obesity may be caused, in part, by deficiency of posterior lobe secretion, though it—like diabetes insipidus—is more especially under control from the hypothalamic area of the brain. More evidence is needed.

FUNCTION OF THE PARS INTERMEDIA

For many years it has been known that posterior lobe extracts contain an active principle which can readily be detected by its influence upon the color of various fishes and amphibia such as the frog. The changeable complexion of these animals is due to the fact that the skin color is determined by special pigment cells, the melanophores, which can expand to produce a diffuse, dark coloration. Or they may contract to minute freckles, leaving the skin otherwise clear. Under the influence of pituitary extract the melanophores expand, thus darkening the skin. Conversely, destruction of the pituitary causes some animals to take on a peculiar silvery appearance. The substance responsible for the change is often referred to as the *melanophore principle*. When it was discovered that this principle was more concentrated in intermediate lobe extracts than in those from the posterior lobe, it began to be suspected that its actual source is the former and that it gets into the posterior lobe only by diffusion. This supposition reached approximate certainty when Geiling showed that posterior lobes from whales, which have the intermediate lobes as anatomically in

dependent structures, are free of melanophore principle It is now generally believed that it is derived from the intermediate lobe, hence it is often referred to as *intermedin* Essentially all that is known of the functions of the pars intermedia is the foregoing fact Since human beings and other higher animals do not have melanophores, this lobe would seem to be of more interest to zoologists than to physicians That the principle has other functions than control of the pigment cells, however, is suggested by the fact that it is obtainable from the glands of many species of animals which lack melanophores It can be detected in the urine of both men and women and it increases during pregnancy in the latter It has been obtained also from certain pituitary tumors (basophilic adenomas) in man

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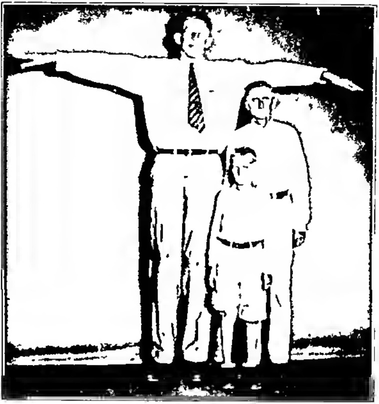


Photograph of a youth of 1[illegible]½ years, standing beside a 9 year old boy and a man who is 5 feet, 11 inches tall. The patient's height was 7 feet, 1 inch, his weight, 278 pounds. His hat size was 7[illegible]8 and his shoes were 17 inches long, estimated as size [illegible]. Courtesy of Dr. L. H. Behrens. Case reported in Endocrinology 16: 120. 1932

A girl of 16 and the same individual at 24 after the onset of pronounced acromegaly She had become almost blind from pituitary tumor From Blumer's Bedside Diagnosis, *courtesy of Dr Hans Lisser and the W B Saunders Co*

Litter mate dogs of which the one on the reader's right re ceived pituitary growth hormone This is a case of true ex perimental acromegaly Courtesy of Dr Tracy J Putnam Reported in Archives of Surgery, 18 *1708 1929*

A case of acromegaly Courtesy of Dr Allan W Rowe

A case of pituitary basophilism in a woman of 43 Her chief complaints were of nervousness, palpitation of the heart, spontaneous bleeding from the skin, flushing of the face and intermittent joint pains Case described by Dr Robert C Moehlig in Jour Am Med Assn 99 1498, 1932

there is no question Its significance in human life will be further indicated in the following section

CLINICAL DISORDERS OF THE PITUITARY

The most definitely characterized pituitary diseases as now known are those due to disturbances of the growth promoting function of the anterior lobe, namely, gigantism, acromegaly, and dwarfism

As recounted in earlier paragraphs, *gigantism* is a condition that has been well known to the layman as well as to the physician for centuries But for purposes of this discussion we must ask the question, where does normal tallness leave off and gigantism begin? A man eight feet in height is at once recognized as a giant, but is one of merely Lincolnian proportions entitled to that designation? Actually, the distinction is not sharply drawn Lisser emphasizes that in true gigantism the abnormal *tallness originates in childhood* It may begin within the first year but commonly arises later The rapidity of growth, however, is likely to increase in adolescence Another fairly common characteristic of giants as compared with normal tall people is deficiency in the sex functions The most sharply definitive sign, though one seldom available for diagnosis during life, is relative increase of the acidophilic cells of the anterior lobe This usually leads to enlargement of the gland itself, often going to the extent of tumor formation

True gigantism is rare The subjects ordinarily attain to a height of six and a half to eight feet Some of the most striking examples are cited in the accompanying table (page 162)

Gigantism tends to run in families and to be more common in some races than in others, Scandinavians seem to contribute more than their proportionate quota The arms and legs as well as the hands and feet of giants are disproportionately long and the shoulders narrow Overgrowth of the pituitary can be recognized in X ray photographs of the skull by the ac

THE TALLEST GIANTS ON RECORD *

Giant	*Author Reporting*	*Height*
Kayanus		9 2 ft.
Winkelmeyer	Virchow	9 0 ft.
Krav	Kiari	8.9 ft.
Konstantin	Dufreny	8.4 ft.
Scotchman	Freulich	8 4 ft.
Austrian	Topiner	8 3 ft.
Alton Giant	(at eighteen)	8.4 ft.

* Cited from Schereschewsky, *Endocrinology*, 10 17 1926

companying changes—especially erosion—in the *sella turcica*, the bony cage in which the gland is contained. The overgrowth may exert pressure on the optic nerves, thus causing defective vision. The early stage of the disease is marked by rapid growth of the skeleton, by excessive muscular strength, and not infrequently by excessive hair growth on the body. Exceptional sex prowess is also common. Occasionally glycosuria (sugar in the urine) is noted. In *later stages* there supervenes evidence of pituitary deficiency such as muscular weakness, sterility, atrophy of the gonads with loss of sex drive, and often adiposity and subnormal temperature. The subjects usually die early Disproportionate enlargement of the internal organs and especially the liver has been found in many of the cases in which post mortem examinations have been made The thyroid, adrenals, and the insulin secreting elements in the pancreas are found to be abnormal in varying degrees If the pituitary enlargement becomes sufficiently great, localized symptoms of brain tumor, such as headache, dizziness, vomiting, or convulsions may occur.

The excessive tallness is due to abnormality of the growth zones in the long bones of the body These structures ordinarily cease to grow ("close up") relatively soon after puberty, but in giants the process is likely to continue well beyond the normal

period This persistence seems to be due, in part at least, to the secondary atrophy of the sex glands, the hormones of which normally bring about closure of the zones

Our knowledge of the disturbances of metabolism that take place in gigantism is defective The basal metabolic rate is frequently abnormal, usually low This datum is difficult to interpret, however, as a diagnostic sign The depression might be due to active protein storage, as shown by Lee in rats treated with growth hormone So interpreted, it would be indicative of pituitary activity On the other hand, the decrease in the basal rate might be taken to measure the secondary depression in the thyroid and adrenals that accompanies regressive stages of the pituitary function Theoretically, during the primary stage of pituitary overactivity the basal rate should be left relatively undisturbed because the lowering effect of the growth hormone should be compensated by the accompanying overactivity in the thyroid and adrenals Disturbances in carbohydrate metabolism should also occur, and actually are frequently found, though specific information is rather scanty In general, it seems to be true that overactivity of the pituitary is marked by decreased tolerance of sugar and, conversely, underactivity by increased tolerance The situation is highly complicated by secondary changes in other endocrine glands, by different degrees of involvement of the constituent lobes of the pituitary itself, and finally by transitional conditions between overactivity and underactivity in these lobes

In gigantism the overgrowth is usually *symmetrical*, but individual parts of the body—for instance, the legs or toes—may be especially affected Rarely one side of the body may be enlarged and the other not (*hemihypertrophy*) From such anomalies it is evident that in this as in other endocrine situations the reactivity of the tissues as well as the hormone concentration is important

The *treatment* of gigantism is not well established Something can be done to stop the increasing height by the use of thyroid to hasten sexual maturity or by the administration of

sex hormone Either procedure may close the epiphyseal junctures in the long bones, but if overproduction of the growth hormone persists the result may be merely the conversion of gigantism to acromegaly If the pituitary overgrowth is sufficiently great as to cause severe pressure symptoms, surgical intervention is indicated Otherwise, most patients prefer the gigantism to the risk of the operation In such cases, treating the gland through the skull with X rays may succeed in slowing down the pituitary growth cells without undue injury to the rest of the pituitary or the brain

Similar in principle and identical, so far as we know, in its fundamental metabolic manifestations is another disorder known as *acromegaly* (Greek *akros*, tip or extremity, *megas*, large) It, too, is due to overactivity of the anterior lobe of the pituitary, followed in the later stages by underactivity It differs from gigantism essentially in the fact that the body has so matured at the time of onset as not to be capable of further symmetrical development The superabundance of tissue that is produced under the stimulating action of the growth hormone is, therefore, confined to those parts of the body that are still able to respond to the stimulation Acromegaly, though a somewhat unusual disease, is not actually rare It is said to occur more often, for example, than does adult myxedema Unlike some other endocrine disorders, it shows no tendency to special geographical distribution No race is known to be more or less susceptible than any other, but Osler is quoted as stating that it occurs rather more often among women than men It begins most commonly in early middle life—and seldom beyond forty—but may arise at any time after late childhood Not infrequently, cases that start before puberty as gigantism are converted to acromegaly at that epoch, being then known as *acromegalic gigantism* Rarely, it may occur in association with precocious puberty, thus, no doubt, is to be explained the occurrence of *childhood acromegaly*, several cases of which have been described The disorder may halt at any stage from the barely perceptible to the full blown form Some hereditary

tendency to it has been reported The condition of pregnancy is likely to aggravate any tendency to acromegaly that may be present, the process may halt with mere coarsening of the facial features

The disease is commonly insidious in its *onset* and slow and prolonged in its *course* Ten to twenty years may be required for its complete evolution Rarely, the course is rapid, leading to fatal outcome within three or four years It may be arrested at any stage, after which the patient stabilizes and from then on may lead essentially a normal life, finally to die of some entirely independent disease But, as Lisser says, "once an acromegalic always an acromegalic, the disease never effaces itself, the person is marked for life, the bony changes remain as indelible clinical fixtures"

Among the *physical findings* in acromegaly the changes in the skull are most striking Often the back of the head becomes markedly elongated, but the facial parts are even more affected The lower jaw enlarges and projects, giving an appearance of elongation to the whole face which has been likened to that of a horse Occasionally only the jaw widens, giving the face a square appearance The tissue underlying the eyebrows become thickened or at least distended by enlargement of the air cells (frontal sinuses) This gives to the eyes a deep-set appearance That fact, together with an encroachment of the scalp hair down onto the forehead, enhances the gorillalike appearance The upper part of the face widens and this adds to the total ugly distortion The nose is always thickened and widened in all directions and may come to be monstrously enlarged, even the tip being enormous and bulbous The nasal bones, cartilages, and soft parts all share in the growth Not to be outdone in the medley of physiognomic exuberance, the ears, too, enlarge The tongue increases in size and may become so huge as to hold the mouth always open The soft palate, uvula, and larynx are also affected so that the speech becomes rather labored and the voice low pitched and hoarse With the growth of the jaws—in which they do not proportionately

share—the teeth gradually become spaced apart, adding to the final ensemble their haglike contribution

Overgrowth is seen likewise in the bones of the upper vertebral column which assumes a bowlike form causing a marked stoop and enlargement of the thoracic cavity The spinal deformity also leads to an awkward protrusion of the face and neck, a posture which the patient assumes to enable him to see ahead when either sitting or walking The bowing of the back also allows the hands to hang low—often to the knees The hump of the back may itself be painful or the distortion of posture may secondarily give rise to lameness and stiffness The gorilla ensemble is further enhanced by the character of the hands They acquire a grotesque, pawlike, or spadelike appearance The wrists are wide and thick and the tapering of the fingers is lost in an enlargement of their outer ends, the typical "tufting of the phalanges" Quite similar changes occur in the feet

The skin shares in the overgrowth, becoming coarse and thickened Normal wrinkles give place to deep furrows But in the final stage atrophy and dryness succeed, hence, in a measure, the furrows are ironed out The hair of the scalp often becomes dense and coarse, the eyebrows shaggy and bushy, the beard heavy and bristly Body hair growth is exaggerated, especially in the region of the lower pelvis and inner sides of the thighs Women share in the hirsutism and may have to endure a heavy beard and mustache, they may be prevented from wearing evening gowns because of the hairiness of the chest and even of the breasts In the later stages of the disease, however, when pituitary deficiency supervenes, the excessive hairiness typically recedes and may even become less than normal

The *symptomatology* of acromegaly is largely obvious from the foregoing description

The patient [as Lisser writes] may seek the physician because he or his friends has noticed disfigurement of the face, with thick-

ening and hypertrophy of the end of the nose and projection of the lower jaw The transformation from refined and delicate features to a massive, coarse, repulsive countenance may take years to develop and take place so gradually that the patient himself or those in daily contact with him are not aware of the transfiguration unless confronted by an old photograph On the other hand, acquaintances who have not seen the patient for a year or more may be astounded on meeting their former friend, especially if the patient be a woman They hardly recognize her because of her distorted and masculinized appearance The patient may have wondered why he is steadily requiring larger hats Women, especially, will be disturbed by the fact that it becomes necessary repeatedly to buy larger gloves Both men and women will notice that they must procure bigger shoes, which enlarge even more in width than they do in length The patient may consult an orthodontist because of the spacing between the teeth

Often the malady develops without any great distress to the subject except as to his sensibilities But it occasionally gives rise to severe rheumatic aches and pains of the extremities, or to excruciating headaches The latter is due in part, if not wholly, to the enlargement of the pituitary that commonly takes place Just as in gigantism, the enlargement may give rise to other pressure symptoms, and especially to defective vision This may vary from slight blurring to complete blindness

In addition to physical symptoms, changes in *temperament* are also fairly common These arise in part, no doubt, from the ever present consciousness of cruel deformity, but in part also, perhaps, from direct effects of hormonal aberration upon the nervous system The patient may recognize the change in personality make up as "inability to get hold of himself" In the earlier stages he may experience wakefulness, moroseness, absent mindedness, inability to concentrate, irritable temper, outbursts of anger, and even homicidal mania During the transition stage, as the pituitary secretion begins to fail, loss of

memory, mental sluggishness, and depression supervene, and finally, if the process is not arrested, apathy, drowsiness, and even stupor—"pituitary hibernation"—characterize the picture

The *endocrine anomalies* in acromegaly are similar to those in gigantism In the pituitary itself the most common abnormality is a tumorlike overgrowth, adenomatous hyperplasia, made up largely of eosinophilic cells Rarely, an excess of chromophobic cells is seen, but they may represent merely depletion of the secretory granules Just as in gigantism, secondary changes are seen in the thyroid, parathyroids, adrenals, and gonads, regression of these structures taking place in later stages of the disease as pituitary failure occurs, or earlier when overgrowth of the eosinophilic cells interferes with the production of hormones other than somatotropin Of the secondary endocrine manifestations, gradual diminution of sexual ardor with final complete loss of libido and potentia may be mentioned In women menstruation becomes irregular, the flow increasingly scanty, and the intermenstrual intervals longer and longer until the function finally ceases These symptoms probably originate immediately in the gonads but express a deficiency of pituitary gonadotropin Adrenal deficiency may be manifested as marked weakness, low blood pressure, and pigmentation The thyroid depression that also frequently occurs ordinarily produces no more than moderate grades of derangement—seldom extending to the stage of myxedema

The *metabolic changes* that occur in acromegaly have not been extensively studied but, generally speaking, are quite similar to those found in gigantism Necessarily, they are highly variable from case to case and from time to time in the same case, mirroring the shifting complexities of the endocrine perturbations of the disease Since the pituitary gland is confined in a rather rigid compartment, overdevelopment of any one lobe is likely to be accompanied by pressure atrophy in other lobes Similarly, within a given lobe increase of one variety of cells must be at the expense of other varieties Thus

the permutations of increased and decreased output of the different pituitary hormones must be numerous Added to this complexity are the secondary changes in glands controlled by the pituitary As a matter of clinical fact, the chief metabolic anomaly that is now recognized is low sugar tolerance—often with glycosuria—in the early stage and increased tolerance later

The *treatment* of acromegaly is the same as that of gigantism

Passing mention may be made of a rare type of growth anomaly known as *infantile hyperpituitarism* It is marked by excessive growth beginning in babyhood Only a few cases have been described Autopsy studies in such cases are lacking, but the only known way in which the abnormality could be produced in such striking degrees as it has occurred is by overproduction of pituitary hormone In addition to the overgrowth, the babies also commonly show excessive fatness Whether this latter manifestation indicates a disturbance in the hypothalamus or deficiency of the posterior lobe secretion is not known

At the other extreme from gigantism we have the condition known as *dwarfism* (*nanosomia*) Midgets have figured largely in folk thought from earliest times Elves, fairies, and gnomes are favorite characters among children the world over The imagination of the weavers of fairy tales no doubt has been stimulated by the existence of human dwarfs

There are several sorts of midgets in which pituitary disturbances play at most only a doubtful role One familiar type, that of the ordinary circus troupe, is the *achondroplastic*, in which the individual grows in some respects to adult proportions but longitudinally is telescoped down to about half the normal size This condition is due to a failure of the cartilages of the body properly to develop into bone. The cause is not known The dwarfing effect of early thyroid deficiency was discussed in a previous chapter On theoretical grounds it might be anticipated that a type due primarily to failure of the

adrenal cortex could be found, but such has not yet been recognized

The true pituitary dwarfism is known as the *Levi-Lorain type* The most common cause of the pituitary failure is infraction (plugging of blood vessels) of the anterior lobe, presumably taking place during the process of one or other of the infectious diseases of childhood Rarely, the destruction is due to tuberculosis or to pressure from near by tumors Very rarely the dwarfism begins before birth or in early infancy Onset between the first and fifth years is less rare, but the most common age is later childhood Sometimes the failure involves only the growth hormone, the gonadotropic and perhaps other gland-controlling hormones being secreted in normal amounts as is true in the case of hereditary dwarfism in mice In that event the individual lives to become essentially a diminutive man He may marry and have offspring—which, incidentally, are likely to escape the parental attenuation But more commonly the sex promoting hormone is also deficient, from which cause the subject is infantile (in the technical sense) and sterile

The pituitary deficiency to which the condition is due may vary widely in degree, hence the subjects may appear as anything from slightly undersized normal individuals to doll like miniatures Similarly, the sex deficiency runs the entire gamut from normality to complete sterility Unlike that of some other types of dwarfism—for example, the thyroid type—the psychic and mental development of the group under discussion may be entirely normal Indeed, some of the most brilliant characters in history have been undersized individuals who were technically dwarfs

The skeleton is always delicately formed The typical childhood proportions of trunk and limb lengths tend to be maintained throughout life The features remain immature The chin is often recessive and the lower teeth fall behind the upper, which latter are apt to be crowded out of alignment The chest is flat and narrow and the protuberant abdomen and low umbilicus of early childhood are retained into adult years

In the earlier years the hair is soft and silky and the skin smooth, delicate, and easily bruised

The *course* of the disorder, in its higher grades, is characteristic At first the dwarf differs little from normal children except for his small size and, usually, retardation in the sex sphere But with advancing age the skin loses its attractive delicacy and becomes wrinkled and pigmented while the face acquires a wizened expression in strange contrast with the size and years The voice remains high pitched The intelligence often fails to mature at a normal rate and the personality early begins to show the effect of the consciousness of being different from normal people Possibly the abnormal hormonal pattern may be a direct factor, also, in the personality structure Usually sooner or later, and often as early as the thirties, premature senility becomes apparent and, with it, often, failure of nutrition (cachexia) Rarely, instead of underweight, obesity develops The condition of premature aging is known as *progeria* Those dwarfs who escape progeria may live out a normal life span, one case is known of survival to the age of ninety-one One of the chief inner signs of halted development is the characteristic failure of the epiphyseal lines of the long bones to close at the usual age of early manhood This condition prolongs the period during which hormone treatment offers hope of amelioration

The *metabolic status* of dwarfs has been relatively little studied The basal rate is reduced and presumably the metabolic pictures are those characteristic of anterior lobe deficiency generally, including abnormalities due to the secondary depressions of the thyroid, adrenal, and sex glands

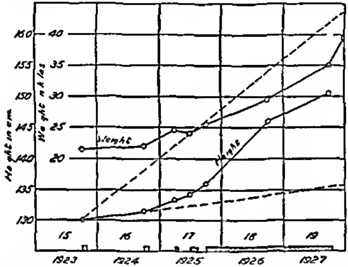
The *diagnosis* of pituitary dwarfism is made largely by exclusion The conditions especially to be differentiated are achondroplasia (chondrodystrophy), primary hypothyroidism, and simple stunting due to defective nutrition The picture of achondroplasia is easily recognized, including as it does large head, saddle nose, and gross lack of symmetry—the arms and legs being greatly reduced in length The hypothyroid dwarf,

as described in a previous chapter, is stupid and misshapen Simple nutritional stunting can usually be recognized by studying the food habits, it is often objectively marked by rickety bowlegs The chief diagnostic criteria of pituitary dwarfism are the normal proportions of the body and the relatively good intelligence The diagnosis can be confirmed by X ray examination This brings out delicacy of the bony structures, generally, as well as characteristic abnormalities of the skull The whole cranium is small but the bones of the face are especially so The skull wall is thin with the inner and outer tables close together and the various sinuses small or absent

The *treatment* of pituitary dwarfism is theoretically simple All that is needed is to supply by injections the missing growth hormone, supplemented, if needed, by sex hormone Practically, the results are usually rather disappointing Occasionally, growth of six to nine inches over a course of one to three years can be induced, but in some cases no response at all is obtained For the professional dwarf who is capitalizing on his abnormality a change of this magnitude, as one once remarked to the author, is worse than none at all, merely detracting from his technical assets without bringing him into the range of the "big people" Empirically, the addition to the pituitary extract of desiccated thyroid in dosage of from one fourth to one grain a day is often helpful Of course, such growth potentiality as there is should be fostered by the use of well balanced, adequate diet and ample supplies of vitamins A, B, C, and D At the present time the cost of potent pituitary extracts is necessarily high and this factor, in itself, denies hormone aid to many Perhaps future research will teach us how to get better results than are now possible Upon the basis of present knowledge, the most satisfactory outcome is in case of those dwarfs who have some innate growth capacity and can be helped to attain a fair approach toward normal adult size Judgment of the efficacy of treatment in such cases is rendered difficult, however, by the possibility, even without hormone medication, of undergoing a considerable "growth spurt" at about the time

of puberty There is always a possibility, therefore, of assigning to the injections credit which is not their due

Dystrophia adiposogenitalis is another clinical disorder in which pituitary deficiency perhaps plays a part The condition is known also as "Frohlich's disease." "Joe," the fat boy in Dickens's *Pickwick Papers*, is a classic prototype The condi-



Graph showing the change in height and weight of a dwarf of fifteen years who took anterior lobe pituitary substance by mouth The rectangles at the bottom of the graph represent periods of medication Courtesy, Dr Allan W Rowe Published in Endocrinology, 12 313 1928

tion is of rather common occurrence and varies widely in its manifestations, depending upon the degree of underlying defect and the time of onset This may take place at any time from early childhood to early maturity To what extent the disorder is actually due to pituitary deficiency and how much to disturbances in the hypothalamic region of the brain is at present a subject of debate among endocrinologists It seems

probable, however, that to whatever extent the pituitary figures in the causation it is the posterior lobe rather more than the anterior that is at fault In a previous paragraph, Smith's failure to evoke obesity by clean-cut destruction of the pituitary as well as his success in producing it by acid injections was mentioned On the other hand, the correction of obesity in this type of disorder by the use of pituitary preparations has been claimed by competent clinicians The various lines of discordant evidence can perhaps best be harmonized by the assumption that the obesity is due primarily to defective functioning of the hypothalamus but that this is projected to greater or less extent by way of the nerve paths into the pituitary

The subjects of the adiposogenital disorder are invariably obese and show depression of the sex function If the disorder takes onset in the earlier years, the genital organs remain underdeveloped If the accompanying deficiency of sex gland hormone prevents closure of the growth zones of the skeleton, development may continue until the eventual size is larger than normal

Excessive thirst, with consequent overproduction of urine, is common The tolerance of carbohydrate food material is increased There may be an almost pathological craving for sweets The underlying cause may cease to operate after a few years and the patient then attain to a condition approaching normality, but the cause is likely to continue so far into adult years as in some degree to fix the condition for life The hands and feet ordinarily remain small and delicate in striking contrast to the rest of the body The excessive fat tends to be characteristically distributed in two zones around the body, namely, at the level of the hips and of the breasts, though the rule is subject to wide variation The mammary gland regions are often strikingly overloaded with fat, which fact, together with the large hips, gives the male a pseudofeminine appearance This is often accentuated by *genu valgum* (knock knees) The skin is often beautifully clear—the "peaches and cream complexion"

The treatment of the condition presents a trying problem to physicians as well as to patients The fundamental reliance in the treatment of all types of obesity is the "first law of thermodynamics"—that is, the law of conservation of matter Fat can be deposited only as it is derived from the food that is consumed The application of the law in such cases is often difficult, however, both because the victims are endowed with an enthusiastic appetite and because they use their food with admirable efficiency Too, they are so blanketed with a heavy layer of fat as to protect them from direct heat loss which is an effective method of dissipating energy Nature employs exactly this arrangement in the layer of blubber with which arctic animals are protected from cold

The utility of pituitary preparations in the treatment of Frohlich's disease is uncertain Many physicians have seen so many failures as to have reached a negativistic position, others, who are more hospitable toward pituitary therapy, emphasize the necessity for large doses and believe that underdosage is a common cause of failure It is not unlikely that varying degrees of primary involvement of the hypothalamus may account for some of the discrepancy of therapeutic results in different hands The accompanying sex depression is more amenable to treatment than is the obesity The supplementary use of thyroid substance is generally advisable

Another disease, the *Laurence Biedl syndrome*, may depend, in part at least, upon pituitary deficiency The disorder was described independently by the two observers by whose joint names it is designated It runs in families if one child is born with it, the brothers and sisters who follow are likely to show the same condition In addition to generalized obesity, the patients are affected with varying degrees of blindness The retina of the eyes shows a peculiar defect marked by excessive pigmentation (*retinitis pigmentosa*) Mental deficiency of greater or less degree is characteristic An accompanying bodily defect that has not been rationally related to the rest of the syndrome is the possession of extra fingers and toes (poly

dactilism) The interesting problem is presented whether de fect in the pituitary—if defect there be—is actually the cause or merely an accompanying manifestation of the disease, so far as is known, this gland has no special relationship either to the retina or to the fingers and toes Treatment has usually been unavailing, but Beck has reported good results from thyroid and pituitary medication Perhaps the best guess that can now be offered is that the disorder originates largely or entirely in some unknown developmental defect of the nervous system

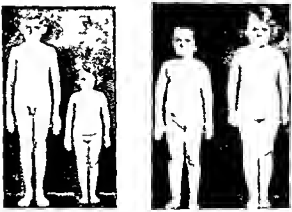
Often occurring in association with Frohlich's disease, but more often independently, is the condition known as *diabetes insipidus* This is a condition that is entirely distinct from dia betes mellitus The latter is due to defective sugar control by insulin, a hormone from the pancreas Diabetes insipidus superficially resembles the pancreatic variety in the copious out put of urine, but it is free of sugar and low in salt content, hence "insipid"

The *cause* of the disorder remained for years a matter of dispute Various data indicated that the posterior lobe might be at fault but it was also known that injury to the hypo thalamus without direct involvement of the pituitary could also produce the disease Even so, however, the urine output could be controlled by injections of posterior lobe extract As early as 1918, von Haam had concluded that diabetes in sipidus in man can occur only if the posterior lobe is func tionally damaged, if the anterior lobe is active, and if the kidneys and circulatory organs are free of serious disorder On experimental evidence, Richter had subsequently concluded that both deficiency of the posterior lobe and at least some functioning anterior lobe tissue are necessary conditions His evidence indicated that the thyroid hormone also plays a role in that thyroidectomy prevented or largely lessened the urine output

The brilliant researches of Ranson and his collaborators have finally clarified the situation By the skillful placement of

A case of pituitary obesity Weight 340 pounds Note small hands and feet Courtesy of Dr Homer Wheelon

Case of Frohlich's disease (hypothalamic pituitary obesity) in a boy of 13 Weight 79 pounds Blood pressure 134 Courtesy of Dr Robert C Moehlig



Pituitary Dwarfism Left hand picture shows the patient standing beside a boy of the same age, 9½ years Right hand picture shows the patient at 9 years and 7 months of age, and 22 months later after treatment with Evan's anterior lobe pituitary extract She had increased 3 inches in height Courtesy of Dr E Kost Shelton

injuries in various parts of the hypothalamus, they have shown that the posterior lobe is controlled by certain brain centers, especially the supraoptic nuclei When these centers are destroyed, or when the nerve tracts leading from them through the infundibulum to the posterior lobe are cut, that structure is no longer able to produce its antidiuretic (water holding) hormone, hence the effect is similar to that of direct gland destruction It appears that when this inhibiting agent is lost the diuretic principle of the anterior lobe can then exert its untrammeled effect of causing excessive urine output

The urine production not infrequently amounts to two or three gallons a day and more than ten gallons has been reported But aside from the annoyance incident to frequent voiding, day and night, the disease is innocuous The excessive urine output gives rise to an equally marked thirst, if water is withheld, this soon becomes genuinely tormenting If sufficient water is taken, the excretory function of the kidney remains adequate, the urine secreted is essentially normal in composition except for its excessive water content If the fluid intake is restricted, however, excretion becomes defective because of the fact that the kidney is unable to put out a concentrated product, hence metabolic wastes tend to accumulate in the blood

The *treatment* of the condition is simple, namely, to supply artificially the missing hormone It can be given by hypodermic injections or by intranasal sprays or in pledgets of cotton inserted in the nose Powdered posterior lobe substance can also be used as a snuff Purified pitressin can be taken, but the unfractionated extract, pituitrin, is less expensive and quite as good.

Excessive urine output is found in another disorder, *Christian's disease* In addition to the polyuria, protrusion of the eyes (*exophthalmos*) and a remarkable thinness of the bones of the skull are also characteristic features In all the cases so far recognized, the disease began in early childhood and the bony defects antedated the diabetes insipidus To a less extent,

other parts of the skeleton share in the defects of the skull The prominence of the eyes, though suggestively similar to that of exophthalmic goiter, is probably merely of mechanical origin resulting from the malformation of the skull To what extent the defect is due to pituitary deficiency is not known The cases so far reported have all followed acute infections, such as scarlet fever

Another disorder which demands consideration is *pituitary cachexia* (emaciation) or *Simmonds' disease* In 1914, Simmonds reported the autopsy findings of a sixty four year-old woman who died in a comatose condition She was extremely emaciated and the body temperature prior to death had been reduced, but no other characteristic symptoms could be recognized She was the mother of five children and had been normal sexually until her last pregnancy, which had been followed by puerperal sepsis (childbed fever) Subsequently, she had never menstruated and had gradually and continuously lost weight during the eleven years that she survived At autopsy no significant abnormalities were found except the general cachexia and complete atrophy of both lobes of the pituitary

Although the disease is relatively rare, forty-one cases had been reliably reported by 1932 (Goldzieher) In the different cases a variety of pathological changes in the pituitary have always been found, but all have had in common practically complete destruction of the anterior lobe This feature implies also atrophy of the thyroid and the adrenal glands, though that condition is not anatomically conspicuous because of the generalized wasting of the body The sex organs are also shrunken, depression of their function is an invariable, and usually an early, symptom

The *course* of the malady may be swift or death may be postponed for many years, but the patient always ages prematurely The most striking characteristic is emaciation—in which the body tissues suffer generally The cachexia with its accompanying weakness is usually progressive It is resistant to all the customary measures for the improvement of nutrition

This general decline is accompanied by, and more or less caused by, a stubborn lack of appetite As the disease progresses there is gradual loss of body hair and decay or falling out of the teeth The skin becomes flabby and wrinkled and acquires an aged appearance The blood pressure gradually becomes low and the heartbeat feeble—conditions due in part, no doubt, to the accompanying adrenal deficiency Increased thirst and consequent voluminous urine are frequently seen in the early stages, but later this phenomenon drops out of the picture The basal metabolic rate is progressively reduced, even more so in the more severe cases than it is in myxedema The body temperature is correspondingly low The blood sugar is reduced and the sugar tolerance high As in other cases of pituitary deficiency, the sensitivity to insulin is increased The proportion of red cells in the blood is below normal Abdominal pains and vomiting are not infrequent additional symptoms The personality deteriorates, loss of alertness and initiative being the first manifestation, then apathy and depression appear, leading at times to a final stuporous psychosis Occasionally the disease may be arrested at any early stage—in which case the symptomatology characteristically persists for years in an attenuated form

True Simmonds' disease has to be differentiated from the psychoneurosis, *anorexia nervosa*, which closely resembles it in symptomatology Unlike the pituitary disorder, however, it often yields to skillful psychotherapy The suggestion is obvious, of course, that anorexia nervosa, though of psychological origin, might be implemented through the pituitary, but the microscope fails to bear out the possibility

The *treatment* of Simmonds' disease has not usually been satisfactory, though good results have been reported in a few cases If the disorder, as appears to be the case, represents pure, generalized anterior lobe deficiency, all that would seem to be necessary would be to supply the various lacking hormones in potent form and in approximately normal proportions This "all," however, is a large one No one yet knows precisely

how many anterior lobe secretions there are, or in what amounts they are discharged from the gland There is good evidence that the proportionate hormone yield from anterior lobe tissue of various species varies widely, hence no one preparation from animal glands could be expected to reproduce the human pattern Whether dried pituitary gland substance by mouth has any value in such cases is a disputed question The more recent experimental evidence increasingly indicates that the anterior lobe hormones are special protein bodies If so, none of them is likely to survive the action of the digestive juices when taken by mouth Various authors have recommended the use of extracts of the glands that are secondarily affected, such as the gonads or thyroid In a few cases adrenal cortex extract has seemed to act favorably Thyroid itself, in small dosages which keep within the anabolic range, may also have some value, but for larger doses the cachexia is a direct contraindication The sex hormones, with their depressing effect on the anterior pituitary, would seem to promise as much harm as help

A major difficulty in the appraisal of the therapeutic claims that have been made is that the psychoneurosis, anorexia nervosa, can so closely mimic pituitary cachexia When success follows the use of gland therapy, therefore, the skeptic can conclude that the case was not one of true pituitary deficiency after all, and that the cure was due to unconscious psychotherapy Whether gland treatment is used or not, the patient should always be given the benefit of an attractive, well balanced diet with full complement of the important vitamins as well as skillful attention to his psychological needs

Another disease that is usually classified as a pituitary disorder is *basophilic adenoma* or *Cushing's syndrome* Some endocrinologists, however, regard it as more of an adrenal than a pituitary disease It was first recognized as a clinical entity by Cushing, who in 1932 reported fourteen cases It is characterized by rapidly developing obesity, the excess fat being confined to the face, neck, and trunk but not affecting the arms and

legs. The subjects soon become round-shouldered—a change that is accompanied by backache. The sexual activities early undergo marked diminution, the women cease to menstruate and the men become impotent. Abnormal hair growth on the face and trunk is seen in women and in preadolescent boys who develop the disease. The skin acquires a dusky, congested appearance and in addition purplish lines (striae). The blood pressure assumes a new, high level. The red cells of the blood tend to increase. The bones lose calcium salts, hence become soft. The blood sugar is increased above normal. Ultimately, to the backache is added abdominal pain and, finally, extreme muscular weakness. In many cases the skin is easily discolored by bruises.

In most of the cases that have been described, the patients were undersized young adults at the time of *onset* The average *duration* of life after the first appearance of the disease in Cushing's series was about five years, though longer survival have been reported by others. Cushing believed that a considerable proportion of the cases of a nature somewhat similar to those just described, which have hitherto been blamed upon the adrenal cortex (adrenal virilism), actually belong in the newer category.

In Cushing's original series, a common finding was overgrowth of the basophilic cells of the anterior pituitary. In some of the more recent cases, however, this basophile-cell change has not been present and a considerable number of instances of basophilic adenoma have been seen at autopsy in which no symptoms of the Cushing syndrome had occurred during life. Rather consistently, there has been found a peculiar hyaline degeneration of the basophilic cells, but this appears to be due to antecedent change in the adrenal cortex (Rasmussen) At any rate, quite regularly the adrenal cortex has been found to be enlarged, and presumably many, if not all, the symptoms of the disease are thereby produced. McQuarrie has called attention to the fact that the blood-electrolyte (salt) pattern in the Cushing syndrome is the opposite to that of Addison's

disease, especially, the potassium is decreased and the sodium increased Harwood and Anderson have furthermore reported evidence of enhanced cortical hormone production in that the blood serum of such patients is capable of prolonging the life of adrenalectomized rats Presumptive evidence of increased cortical activity is seen, too, in the fact that sex hormones, both male and female, are excreted in amounts higher than normal That the sex glands, parathyroids, and perhaps the islands of Langerhans of the pancreas are also involved is believed by several students of the disorder, though symptoms rather than microscopic appearances in the suspected glands are cited chiefly in evidence Altogether, the weight of the evidence tempts to a theory that the Cushing syndrome is caused primarily by exaggerated activity of the adrenal cortex and that this is due often, but not always, to augmented output of adrenotropic pituitary hormone

The *treatment* of the disorder is as yet uncertain A considerable number of cures have been reported from X ray administration addressed to the hypophysis Radiation of the adrenals is recommended as a supplementary procedure (Pardee) The injection of estrogenic hormone for the purpose of depressing the anterior lobe has also its proponents who claim favorable results Surgical removal of redundant adrenal cortex tissue has theoretical warrant but is a resource to be used only with the greatest caution because of danger to life

Finally, one of the most important disorders due to anterior lobe deficiency is *pituitary infantilism* This results from inadequate production of gonadotropic hormone Since the manifestations are very similar to those of primary sex gland deficiency, however, further discussion of the subject will be deferred to later chapters

RELATION OF THE PITUITARY TO PERSONALITY

That pituitary defects and temperamental anomalies are sometimes associated is well known But there is no scientific

justification for the extravagant claims that have been made that the pituitary commonly dominates the whole personality, nor for the specificity of relationships that has sometimes been claimed.

One school of anthropologists, led by such men as Kretschmer, Pende, and Bauer, believes that the personality of the individual is largely determined by his *constitution*. While the constitution is determined fundamentally by genetic factors, these express themselves to greater or less degrees through the endocrine glands. Furthermore, various environmental influences may also express themselves through the same agencies. Of all the endocrine structures, the pituitary, with its wide, special influences on the metabolic processes and on the other glands, seems to be the most significant in determining constitution. We are prepared, therefore, on a priori grounds to extend mental hospitality to any concrete evidence that can be brought forth regarding pituitary factors in personality.

Mayers, who has made a special study of the subject, reports that oversecretion of growth hormone as seen in acromegalics leads to intensive living with courage, initiative, and forcefulness of character as outstanding traits. Then later, as the secretion wanes, timidity, lassitude, and failure follow. Collip has described the case of a wolfhound puppy from which the pituitary was removed. From an aggressive, pugnacious creature it was converted to a whimpering coward. When treatment with pituitary extract was instituted, much of its former behavior was restored. In the rat, as Richter has shown, removal of the pituitary causes marked lessening of activity, reduced interest in food and water, and a completely platonic attitude toward members of the opposite sex. These changes are ascribed to the influence of the operation upon the adrenal and thyroid glands. The only augmented activity was that of nest building—another reaction to the secondary thyroid deficiency that left the animals sensitive to cold. In most cases of experimental pituitary deficiency, however, changes of temperament have not been sufficient to lead to remark in reports of the experi-

ments Smith explicitly states that monkeys ordinarily show little change in temperament or behavior following removal of their hypophyses Human dwarfs who have lacked anterior lobe hormone from early years, contrary to the picture seen in secondary failure of acromegaly, are commonly rather aggressive, but become so perhaps chiefly or entirely as a matter of overcompensation for their littleness

In the sex sphere the hypophysis plays an unquestioned and important role It follows, therefore, that indirectly, at least, such aspects of personality as are determined by the gonadal hormones are importantly influenced The topic is discussed in further detail in other sections of this work

In addition to its effect on milk production, the anterior lobe product *prolactin* has a striking influence on animal behavior It induces broodiness in the fowl and modifies the nesting behavior in certain fish (Riddle) Its influence on the instinctual behavior of rats has been studied by Wiesner and Sheard and by Riddle

The method of procedure is to place young female rats in cages with materials for nest building They are then tested as to the strength of their maternal urge by being offered newborn baby rats for adoption In most instances the females remain indifferent to the intruders But if, to these nonchalant misses, a few doses of prolactin are administered, not only are their mammary glands stimulated but a remarkable change in their behavior takes place They will now eagerly adopt as many babies as may be offered, build elaborate nests for them, and eagerly mother them The yearning seems to be universal Their maternal reactions are not confined to infants of their own kind but are extended to baby mice, baby rabbits, or even helpless squabs For a normal, vigorous rat to do other than promptly make a feast of a proffered squab is proof positive that something fundamental has happened to her instincts What part prolactin may play in the determination of human instincts and emotions is as yet unknown, but the stimulus to

imagination is tempting. To what extent is mother love a matter of hormone chemistry? Could prolactin convert a cold misanthrope into a lover of his kind? Should our predatory overlords be sentenced to a course of prolactin? Such questions might be multiplied and they are not entirely fanciful. One wonders whether the folk phrase, "the milk of human kindness," betokens a vague foresensing of the functions of prolactin.

These observations are of no little theoretical importance. So far as one can judge of rodent personality, prolactin goes deep and makes a fundamental modification. On one day the rat presents an energy system that reacts in a characteristic set of behavior patterns. A week later the same rat shows behavior patterns that are grossly different. Similarly permeative changes can be induced by the sex hormones. The reacting organs are the same, the available energy of the system is the same. Whence then comes the difference? The phenomena seem to necessitate the recognition of a new, far reaching biological principle, that of *chemical conditioning*. The results are comparable to, and in the last analysis possibly identical with, those of the more familiar type of conditioning that is emphasized by psychologists. That one learns by experience has long been known. It is now apparent that one may also "learn"—and in a profound way—by the injection of a hormone. A study of the influence of prolactin on the emotional experiences of women to whom it is given for therapeutic purposes might bring out important data. A problem that might appeal to psychoanalysts is also suggested.

As pointed out in an earlier section, the fat boy disorder, *dystrophia adiposogenitalis*, seems to be determined, in part at least, by pituitary deficiency. In this disorder excessive sleepiness (pathological somnolence) is frequently seen—"Joe! Joe! Damn the boy," wrote Dickens, "he is asleep again!" Lurie reports that children of this type are in general of a compliant passive submissive temperament but may be-

come so resentful of the ill natured gibes of their playmates as to become aggressively sadistic in an attempt to get even with the world

It is the adiposogenital group who have figured mostly in the reports that have been made on specific relationships of the pituitary to personality In one such study—by Rowe—of six hundred and fifty children, abnormal pituitary function was diagnosed in two hundred and seventy nine Among these latter, behavior problems had been encountered in fifty three The aberrations consisted of such manifestations as moroseness, bullying, disobedience, lying, thieving, and vagrancy Grouping the data in another way, it was found that of the one hundred and four children of the total series who presented behavior problems, two thirds showed evidence of endocrine abnormalities In the great majority of these children, the pituitary was diagnosed as the gland at fault In a similar study, Lurie diagnosed pituitary disorder as the predominant abnormality in ninety three patients showing both endocrine disturbances and behavior difficulties In a considerable number of cases in Rowe's series, as well as in Lurie's, pituitary material was administered, following which the personality defects often improved Occasionally, similar results have been reported from other sources Generally speaking, however, such therapeutic studies have not been properly controlled, mere coincidence has not been satisfactorily excluded as accounting for such favorable changes as were seen Furthermore, how much moral suasion was administered with the pituitary was not stated, hence we are at a loss to know what credit should go to the gland medication

Several investigators have reported that the pituitary glands of *psychotic patients* are commonly abnormal Cushing at one time examined seventy pituitaries from state hospital subjects without finding a single normal gland The alterations consist commonly of excess of connective tissue—a common finding in degenerated glands—or disproportion of cell types, but no consistent relationship between any particular microscopic pic

ture and any particular psychosis has yet been determined Tucker has described a "pituitary psychosis" which, he believes, originated in a deficient secretion of the gland, as evidence, he reports amelioration following pituitary medication The disorder was described as generally resembling dementia praecox, but an unusual element of hysteria was also present Too, some observers postulate pituitary disturbance as one factor in the production of epilepsy, a condition likewise often characterized by profound changes in the personality

For the most part, endocrinologists who have been concerned with the pituitary have been little interested in the psychological aspects of the subject Conversely, few well trained psychologists have found their productive interests in the endocrine field When better working liaison between endocrinology and psychology shall have been attained, it is not unlikely that much more will be learned of the relationship of the pituitary to personality In the meanwhile, a conservative attitude seems desirable

CONTROL OF THE PITUITARY

Despite the fact that the pituitary gland is one of the most important controlling mechanisms of the body and, as such, has been the subject of a very large number of researches, our knowledge of how it, itself, is controlled remains notably inadequate The situation presents the same paradox that is seen in case of the thyroid gland, namely, that it is to some extent subject to nervous control but is also able, when removed from such control and implanted as a graft, to sustain bodily functions that are dependent upon its secretions One major difficulty in interpretation is the current uncertainty as to the precise relationships that exist between the gland and the adjoining parts of the brain Injuries of the hypothalamus, produced experimentally, by accident, or by the growth of tumors, have been shown to lead to such disturbances as obesity, excessive urine formation, and abnormalities of sugar metabo-

lism Similar disorders are producible experimentally by injuries of the pituitary There is some evidence also that from the brain tissue in the hypothalamic region can be obtained by active extracts that share in the properties of pituitary derivatives—and, indeed, secreting cells in this part of the brain have been described A third paradoxical element in the situation is that severe injuries of the hypothalamus may either produce the abnormalities just mentioned or may result in no detectable disturbance of function whatever

A long series of investigations, culminating in the brilliant work of the Ranson group, has shown that the *posterior lobe* is under direct control from the hypothalamus Thus, polyuria can be brought about either by the destruction of the lobe itself or by interrupting the nerve paths from the controlling brain centers The evidence, however, refers primarily to the vasopressor principle Whether oxytocin is similarly controlled is not clear Furthermore, we are relatively uninformed as to the influences which impinge upon the hypothalamic centers, but Chang (1937) has shown that stimulation of the vagus nerve causes increased output of the vasopressor principle and presumably this influence is centrally mediated There is evidence that the amount of water-controlling (antidiuretic) principle secreted varies with the water intake Presumably, therefore, the degree of dilution of the blood influences the rate of posterior lobe secretion Whether the influence is mediated reflexly or directly upon the hypothalamic centers or upon the gland cells themselves is not known

Although the nerve supply of the *anterior lobe* is scanty it, too, appears to be to some extent under nervous control The fact that various endocrine anomalies can be produced by minute tumors in the hypothalamic region suggests that the anterior lobe is under immediate control by brain centers as is the posterior lobe, but direct evidence is scanty Interrupting the nerve path by destruction of the superior cervical ganglia of the sympathetic system has been reported to cause disappearance of the acidophilic cells in the anterior lobe As stated

in a previous chapter, the experiment is occasionally successful when a phrenic nerve is grafted into the superior cervical nerve, thus shifting the breathing impulses to a new target organ The evidences of enhanced thyroid activity thus brought about were ascribed by Cannon to a direct influence upon the thyroid gland Subsequent work in his laboratory (Friedgood) led to the conclusion that the thyroid effect is brought about through the agency of the anterior pituitary, which finding affords further evidence that this structure is under sympathetic control Additional evidence of reflex control of the anterior lobe is seen in the fact that in some animals (rabbits) eggs are normally discharged from the ovaries only after the act of coitus, the extrusion can be induced artificially by mechanical stimulation of the cervix of the uterus There is evidence that this reflex is carried out, in part at least, through the sympathetic nervous system, but the final path of the impulses is through the infundibular stalk

In many animals—amphibians, birds, and mammals—the sexual cycles are strongly influenced through the pituitary by the amount and quality of the light to which the creatures are exposed (Bissonnette) In some cases, at least, destroying the eyes or cutting the optic nerves abolishes the reaction Furthermore, in some it can be set up by direct stimulation of the cut optic nerves This mechanism is of special importance in animals which show a seasonal periodicity in their reproductive activity An interesting commercial application of the principle is to increase egg production by hens in winter by subjecting them to night lighting In ferrets, even the seasonal shedding of hair is determined by the light cycles acting via the pituitary Bissonnette believes that the posterior lobe as well as the anterior lobe is subject to light control

The fact that the anterior pituitary demonstrably stands in reciprocal relationship with various other endocrine glands means, of course, that the hormones from these latter exercise a controlling influence, direct or indirect, upon that gland itself As a general principle, it seems that when any gland which

derives a stimulating hormone from the pituitary becomes underfunctional the secretion of that hormone is augmented. Thus, after castration the anterior pituitary produces more gonadotropic hormone. Conversely, the administration of sex gland hormones leads to decrease of the gonadotropic secretion. The adrenal cortex and the thyroid appear to sustain a similar relationship.

Such evidence, however, permits no deductions as to whether the relationship is maintained through the agency of the nervous system or through direct reciprocal influences upon the producing cells of the different glands. In case of the adrenal cortex, the control seems to be direct because cutting either the pituitary stalk or the cervical sympathetic nerves prevents the adrenals from hypertrophying when the animal is exposed to cold. On the other hand, in case of the thyroid the control seems to be mediated through the hypothalamus because cutting the pituitary stalk prevents thyroid hypertrophy under similar conditions (Uotila, 1939).

The fact that the pituitary exercises a multifarious control over the metabolic processes of the body suggests that the gland may react adaptively to a variety of shifts in the metabolic patterns of the blood with which it is fed Thus, low blood sugar might, by direct action, call out an augmented secretion of the anti insulin factor and reduced water content of the blood call out antidiuretic hormone. Whether, as a matter of fact, this possibility is widely utilized remains unknown.

In view of the large biological issues that are at stake, there are few aspects of endocrinology more in need of further study than is the problem of control of the pituitary gland.

THE BIOLOGY OF THE PITUITARY

From the evidence now available, it is obvious that the pituitary gland plays a large role—possibly a predominant role—in the regulation of the physiological processes of the

body Directly or indirectly it influences, too, the mental activities, at least in so far as these are under direct thyroid control In whatever degree the personality is determined by somatic and mental influences this, too, must be modified by the pituitary This gland profoundly influences the metabolism of the three principal foodstuffs—proteins, carbohydrates, and fats—and by its influence on nutrition affects all of those manifestations of energy that go to make up life itself

But how all of these influences are mediated, what are the intrinsic limitations of the mechanisms involved, we can often only surmise The general problem of pituitary functions breaks up into a multitude of component problems A large number of these are under intensive investigation in laboratories and clinics throughout the world But many years must necessarily elapse before many of the solutions can be expected Despite the world wide interest in the subject of endocrinology, the competent productive investigators in the field are numbered only by hundreds—not by thousands as popularly supposed

In approaching the problem of the adaptive significance of the pituitary we may ask in what respects life is more efficient with than without it What advantage is there, for instance, in having our stature left at the mercy of the growth hormone? The growth process in itself can take place without benefit of hormones, as seen in tissue cultures and in the early stages of the development of eggs In many of the lower forms nothing comparable to somatotropin has been discovered

Perhaps in the last analysis the pituitary in its relationship to growth and other metabolic processes serves merely as a diffuse mediator of nerve impulses and thus as a conservator of energy The same general principle may be invoked to account for the control of other endocrine glands by pituitary hormones As is evident from the fatigue which arises in cases of imbalance of the eye muscle with resulting continuous calls upon the nervous system for correcting impulses, nervous control is expensive to the organism On the other hand, the

process of secretion is much less so For example, as long as the food supply is adequate a cow can continue to produce milk in large quantities with no break in her proverbial placid contentment Thus, by turning a large part of the job of controlling the endocrine glands over to the anterior pituitary nature perhaps has achieved an effective economy

In case of the sex glands, as will be discussed in subsequent chapters, the interpolation of the anterior pituitary in the reacting system provides a mechanism for securing cyclic behavior This is seen especially in the menstrual periodicity, underactivity of the gonads brings about overactivity in the production of gonadotropic hormones and vice versa Were these countervailing impulses too delicately balanced, a state of equilibrium would soon be reached and maintained But by the introduction of a lag in response—hysteresis, in terms of the physicist—periodicity in the conditions of underactivity and overactivity is achieved

Perhaps the clearest manifestation of the adaptive value of the pituitary, as now known, is seen in its control of water metabolism This process, as mentioned earlier, seems to be determined at any given moment by the balanced action of a diuretic principle in the anterior lobe and an antidiuretic principle in the posterior lobe When water is taken copiously, the diuretic principle is secreted in relative excess, and when water depletion threatens, the antidiuretic principle is produced to check the fluid loss The possible excitement of similar mechanisms for the control of other metabolic processes was mentioned in the preceding section

That the oxytocic principle of the posterior lobe is an important agent in bringing about the onset of labor has often been surmised, but the evidence does not yet permit definite judgment on the point The mechanism theoretically could operate in either one of two ways The secretion rate could gradually build up during the progress of the pregnancy to a point at which a reaction threshold would be overtopped, or the secretion rate might remain constant and the sensitivity of

the uterus be gradually increased to the point at which the emptying response is obtained Such evidence as there is points rather to the second alternative

That the pituitary gland is of the utmost importance in the regulation of the vital processes is evident from the symptomatology of any case of Simmonds' disease, as well as from many evidences besides The fact that the pituitary is a going institution in so many species of animals indicates that its possession confers substantial advantages upon its possessor But the exact ways in which the advantages are reaped remains largely for future researches to determine

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VI. THE MALE SEX GLANDS—THE TESTES

In the folk thought of all times the testes have figured as the source of virility Not only because of the resulting sterility, but even more, perhaps, because of the effect upon the personality of the subject, emasculation has always been regarded as a major calamity From time immemorial removal of the testes, *castration*, has been practiced on the common farm animals as well as human beings The operation has been a religious rite among various sects—for example, until recently the Skoptzs of Russia The *eunuch* thus produced has had a special utility in various organizations of society, particularly as guardians of harems As late as 1870, the operation was practiced to conserve the high pitched singing voice of boys of a famous choir It was from observations of individuals who had undergone such mutilation that the popular impression was derived

Sex has been defined as "the sum of the peculiarities of structure and function that distinguish a male from a female organism " A considerable part of these peculiarities has only indirectly to do with reproduction A distinction must be made then between sex, as such, and reproduction, as such The male gonads, the testes, have intimate relationships with both These glands perform a dual function Not only do they produce the male fertilizing elements, the *spermatozoa*, but likewise one or more hormones that have to do with the many physiological and psychological adjustments by which the function of reproduction is carried out

Sex and reproduction, though ultimately directed toward the same end, differ in various fundamental respects *Reproduction* has been defined as "those processes by which life is continued from generation to generation" Actually, in many of the lower forms reproduction is carried on by processes that are not sexual These amount, in effect, merely to the separation of a portion of its substance from the parent body, which portion then continues existence as an independent unit The propagation of geranium plants by the use of "slips" is a case in point Potato growers cut one tuber into several portions from which new individual plants arise Many of the lowest forms of animal life simply grow until the ratio of surface to mass becomes too low for individual efficiency, whereupon the creature divides into two and the halves go their separate ways to repeat the process when they, in turn, come to have too small a surface for the living bulk within Bacteria attain essentially the same end by forming concentrated bits of body substance, the spores, that are cast off and set up independent existence

Sexual reproduction always involves the junction and blending of two cells from different individuals. The composite thus formed then develops into the finished organism In the lowest types of animal life, such as the paramecia, the blending takes place between the two parent organisms as entire individuals, by the process known as conjugation In the higher forms, individual sex cells are separated off and it is these that unite The process of union is known as *fertilization*

Early in the evolution of the higher forms the reproductive tissue from which the sex cells arise was set apart from the body tissue in the form of *gonads* The gonad substance, the *germ plasm*, is carried from generation to generation in rather complete independence of the other body cells One type of gonad produces the male sex cells, the spermatozoa, the other, the female cells or *ova* (eggs) Ordinarily, the possessors of the two sorts of gonads are separate individuals that differ more or less in their characteristics Both types of sex glands, however, may occur in the same individual, and in some species

the males and the females are scarcely distinguishable There is not actually the sharp differentiation between maleness and femaleness that is commonly assumed In many forms, including the human species, each individual represents a blend of male and female characteristics of varying grades

The segregation of the sex cells in two types of gonads has rendered necessary a variety of mechanisms for bringing the germinal elements together Nature's simplest solution of the problem is seen in such animals as the fishes, which merely extrude the ova and the spermatozoa into the water in which both parents live The spermatozoa are actively motile and in their random movements make contact with the ova with which they fuse The only accessory mechanism is the instinct of the parents which leads them to deposit the two kinds of sex cells in the same locality In many forms an intricate variety of bodily, psychological, and social adaptations has been evolved whereby the sex cells (*gametes*) are brought together

Wheelon has defined sex as "dependent upon the sum total of the somatic characteristics and differences associated with the reproductive tissue" He continues "In addition to the evolution of male and female genital organs arose other phenomena by which the sexes are characterized Such features were designated by John Hunter as *secondary sexual characteristics* This term embraces all those specific differences between the male and the female which are not directly concerned with the processes of reproduction" Such characters are usually more elaborate in the male than in the female Familiar examples of these characters are found in insects and vertebrates, but they are rare or absent in the lower invertebrates The horns of the stag, the mane of the lion, the great variation of color among birds, the phosphorescent organs of the firefly, and the distribution of hair in man—as well as its propensity to early departure in males—are typical examples of secondary sexual characteristics

In addition to the anatomical and physiological differences

between males and females, there have arisen also distinctive sexual *instincts* In the higher forms these include the impulses that bring the male and female together at the breeding season They control the behavior of the individuals in their reciprocal relationships, such as courting and mating Finally, they initiate the various activities involved in the building of nests and the rearing of the young In many animals the sexual instincts are operative only during the breeding season The utility of this adaptation is obviously to insure that offspring will not be produced at unfavorable times of the year Various of the secondary sex characteristics, too, are exaggerated during the breeding season only to wane with its passing In many of the higher forms the periodical changes in the secondary sex characteristics are under the immediate control of the primary sex glands

THE ANATOMY OF THE TESTES

The testes are paired organs which throughout the higher vertebrate series of animals conform rather closely to a standard pattern In man they are elongated ovid structures somewhat thicker in one transverse diameter than in the other They are about the size of a small hen's egg They are contained in an extension of the body cavity which is surrounded by continuations of the various layers of the abdominal wall to form a sac, the *scrotum*

Each testis is enveloped in an outer covering, the *tunica vaginalis*, which is structurally similar to the peritoneal lining of the abdominal cavity of which it is a localized extension At the posterior aspect of the gonad is attached a supplementary structure, the *epididymis* This is a tube which is complexly folded back and forth upon itself to form a head, body, and tail Underneath the outer tunica the testis is surrounded by two other membranes the dense white inelastic capsule, the *tunica albuginea*, and an inmost layer, the looser and more vascular, *tunica vasculosa* The tunica albuginea extends inward from the posterior aspect of the gland to

form a dividing partition or septum From the sides and front of the septum secondary partitions extend to divide the organ further into a series of compartments, each occupied by a testicular *lobule* The number of lobules varies in man from about two hundred and fifty to four hundred The lobules are composed of minute *seminiferous tubules* in which the sperm cells are formed The tubules are embedded in loose connective tissue within which is packed the *interstitial tissue*, made up of the *cells of Leydig* The tubules lie in the form of loops which join at their ends to form *straight tubes* through which their products are discharged The straight tubes lead to a network of secondary tubes within the median partition known as the *rete testis* The tubes of the rete finally converge into the *efferent ducts* Through these the secretion passes to and through the epididymis to enter the final conducting tube, the *vas deferens* The vas, coursing within the *spermatic cord*, carries the secretion upward into the abdominal cavity to be finally stored in the *seminal vesicles* From these repositories the testicular secretion with addition of contributions from the vesicles and the *prostate*, is discharged as the fertilizing *seminal fluid*

The testis derives its *blood supply* from the spermatic branch of the superior vesicle artery which comes off directly from the aorta The venous blood is returned through a network of veins, the *pampiniform plexus*, which proceeds upward into the spermatic cord The lymphatic drainage is through this same cord to the lumbar lymph nodes The front and sides of the testis get their *nerve supply* from the genitofemoral nerve, the posterior surface from the perineal branch of the pudendal, and the inferior surface from the perineal branches of the posterior femoral cutaneous nerve

The *embryonic development* of the testis is a rather complex process The first indication of the oncoming gonads, whether testes or ovaries, is seen when the embryo is about a fourth of an inch long, appearing as an inconspicuous pair of elongated swellings, the *genital folds* These project, on each

side, into the primitive body cavity near the site of origin of the adrenal glands By the time the embryo has doubled in length the primitive gonad is a fairly conspicuous protruding cellular mass After the first month of development the testes and ovaries can be differentiated by the increasingly characteristic arrangement of the component cells, though both the male and the female structures are laid down in rudimentary form in each

At first the protruding cell mass appears to be rather uniform in its structure, but at about the sixth week the cells in the male begin to condense in certain places to form the rather irregular *testis cords* which are separated by looser bands, the *intermediate cords* The testis cords are arranged in radial fashion to converge in what becomes later the rete testis The cords consist of two kinds of cells, the *indifferent* and the *genitaloid* During the seventh month the testis cords are converted into tubes which finally form the adult arrangement described above The structures then lie dormant until the time of puberty when the cells within the seminiferous tubules begin to multiply to form the spermatozoa The *cells of Leydig* arise from the genitaloid cells of the intermediate cords They are relatively very numerous from the mid foetal period until after birth but degenerate afterward until, at the time of puberty, they again increase in numbers to form the interstitial tissue The foregoing orienting sketch omits many details which may be found in textbooks devoted to anatomy or embryology

During the earlier period of development the testes remain high in the abdominal cavity, immediately beneath the diaphragm, but about the third month they begin to descend toward their final position in the scrotal sac. The final departure to the exterior takes place at about the time of birth At this time the glands are about the size of small almonds The passages through which they penetrate the body wall remain open throughout life in some animals, such as the rat, but in

man and most other higher forms the openings are obliterated The body wall remains rather weak at these points, however, and not infrequently ruptures later in life to form hernias

Occasionally the testes fail to complete their migration out of the body cavity In that case we have the condition known clinically as *cryptorchidism* It is from this fact that one important piece of endocrine knowledge is derived The sex cells in the cryptorchid testis do not progress beyond the infantile stage, hence the subjects are always sterile They may have, however, their full complement of masculine vigor and often succeed in developing normal secondary sex characters For example, beard growth takes place at the proper time and the voice undergoes the normal change from the piping treble of youth to the lower pitch of manhood We seek elsewhere, therefore, than in the generative tissue proper, for the source of the hormone that brings about the bodily—and indeed the psychic—changes of puberty By exclusion, this function is ascribed to the interstitial cells of Leydig The microscope supports the deduction The Leydig cells in those cases in which the sex structures are found to be normal are themselves also normal

For many years no reason could be assigned for the failure of the sex cells to develop when the migration of the testis fails to occur The imprisoned organ receives its normal blood and nerve supply and there was no apparent reason why it should not fare as well functionally as do the other internal organs It was then discovered that the sex cells are especially susceptible to the action of heat The experimental animal, and presumably the human male, can be effectively sterilized by a few hours' application of a degree of heat as mild as that normally existing within the body cavity The matter seems not to have been formally investigated, but it is probable that an attack of fever commonly sterilizes a man until the testis cells have had time to recover from the period of elevated temperature This susceptibility might be used as a harmless method of intentional sterilization Though this possibility has

not been investigated in man, it has proved practicable in sheep The actual significance of the heat-susceptibility of the generative tissue is not known One might theorize to the effect that it is a protective device to forestall propagation by fertilizing cells that had been injured by toxins that produce fever—cells that might give rise to defective offspring—but that would be sheer guess work. Whatever the explanation may be, the curious fact remains that the sex cells do not develop until the gonad escapes from the body cavity

PREPUBERAL ACTIVITY OF THE GONADS

The testis definitely has the function of producing the hormone or hormones that bring about the far reaching changes characteristic of puberty Does it have any hormone function in the earlier years? Although the child is largely neutral, sexually, there are certain differences between the male and the female even at this age that suggest the operation of a hormone factor in one sex or the other The best evidence that the testis early assumes a function of internal secretion is derived from observations by cattle breeders It happens occasionally that cows give birth to twin calves of opposite sex, the blood streams of which intermingle through the placental tissues by which they are attached to the uterus The female of the pair becomes marked for life with a stamp of masculinity from which she never recovers The *free martin* thus formed assumes in part the configuration of the male The mammary glands and the internal female sexual structures remain undeveloped while the rudimentary male structures are accentuated Thus, life long sterility arises A plausible explanation is that the erst while female during the fetal period was so inundated with the male hormone of the twin brother as to have received a permanent masculine impress Similar *sex intergrades* can be produced in rats, as Ivy has shown, by injecting pregnant mothers with an excess of female hormone Their male offspring are substantially, though not completely, feminized,

the male sex rudiments being depressed and the female rudiments stimulated

GONAD DEFICIENCY—EUNUCHISM

Acute gonad deficiency is a condition that is intentionally set up in many millions of animals each year In farm practice, *castration* of the males is a common procedure The operation is performed to promote docility as well as to bring about metabolic changes that add to the value of the animal for food In man, the condition of complete testicular deficiency is known as *eunuchism* Partial deficiency results in *eunuchoidism*

As to the outstanding final results of castration there is common agreement The subjects, human or lower animals, continue to grow to, or beyond, adult proportions but fail entirely to undergo the bodily and psychic changes of normal puberty The resulting state, in large measure at least, represents merely a persistence of a neutral asexual form, an expression of the growth impulse of the body itself without the operation of sex hormone Common observation, however, suggests that the prepuberal is not entirely a sexless stage The boy early shows a certain degree of robustness, both physiological and temperamental, that rather sets him off from the girl of the same age It must be recognized, however, that many a ten year-old girl concedes nothing to her brother on either score Accurate judgment as regards the psychological aspects of the situation is difficult because of the operation of social factors, though less so now than in the past Consciously or unconsciously, almost from infancy efforts are directed to fit the little girl for a "woman's place in life" and, conversely, her brother to be a "real man"

More fundamentally considered, an intricate problem is presented The actual sex of the individual is determined at the moment of conception by the chromosome make up of the gametes This constitutional difference is transmitted to all the body cells that result from the fertilization Since the very body cells of the female differ from those of the male, there is,

a priori, no need to assume the operation of a hormone as an additional *sex determinant* Many examples are known in which an innate developmental impulse lies latent until the proper time for its expression arrives Such a principle might be invoked to account for the evolution of masculinity at any stage Nevertheless, the evidence is clear that to no little degree it is the flooding of the body cells with sex hormones that actually does determine the end result The body-cell constitution seems to play a relatively slight role in the evolution of sex, in reality the individual is thereby endowed only with the potentiality of sexual development

In large degree, the early organism is, in effect, neutral and can be turned toward the male or the female course by circumstances Indeed, within fairly wide limits, the male can be transformed to a female and vice versa Riddle has discussed the subject at length Among many other examples of *sex reversal* he cites the well authenticated case of a fowl that succeeded successively in being both a mother and a father In an earlier stage fertile eggs were produced Then the ovary became diseased and a rudiment of a testis developed into a functioning organ that produced fertile male cells This phenomenon has been observed in several kinds of birds

The organism at birth, then, has large potentiality of proceeding toward either sexual goal The problem of the relative significance of constitutional and of hormone factors in the final outcome must be solved empirically It can be profitably studied by contrasting the results of allowing development to proceed when the hormone factors are present and when they are absent Likewise significant are the effects of eliminating the hormones after the sex characteristics have become established

Occasionally it happens either through accident or disease—and especially mumps—that the testes of boys are injured or destroyed Until the age of puberty certainly no very striking defects other than in the gonads themselves can be detected But with the arrival of the period of normal transition to man

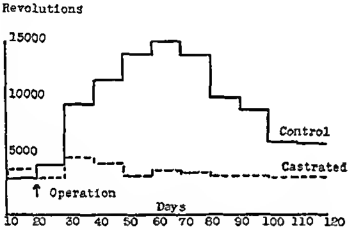
hood the effect of the testicular deficiency becomes, in a negative sense, profoundly evident The boy fails to develop many of the characteristics of his normal adult kind The voice remains high pitched The beard fails to appear Hair growth also fails to take place to a normal extent under the arms and over the body generally The pubic hair either fails to appear or shows the pattern of the female and in scanty amount The primary sex organs, the phallus and the prostate, remain underdeveloped The growth zones of the bones remain open and the long bones continue to increase in length even well into the third decade Thus, as a rule, the subjects become unusually tall The bones are slow, too, in acquiring their adult proportions of the mineral elements, lime and phosphorus There is some evidence that the thyroid gland fails of normal development and the thymus tends to persist as in childhood The more obvious results of testicular failure in youth were picturesquely set forth in a passage cited by Lisser from Chaucer's *Canterbury Tales*

> A voys he hadde as small as hath a goot
> No berd hadde he, ne never sholde have
> As smothe it was as it were late y-shave
> I trow he were a gelding or a mare

The metabolic effects of testicular deficiency are not striking There is a tendency, however, toward low blood pressure and reduced oxygen consumption A certain flabbiness of the muscles as well as reduction of nitrogen output in the urine indicates an interference with protein metabolism This is often indicated, too, by more than the normal output of creatine In man, the metabolic defects may result in a generalized failure of nutrition, giving rise to the thin type of eunuch, but more commonly the subjects become obese Actually, the chief reason for castrating food animals is to facilitate their taking on fat In addition, however, the overgrowth and flabbiness of the musculature—in housewives' parlance, "tenderness of the

meat"—are desired features As a well known example, the *capon*, which is a castrated cock, is an expensively more desirable table bird than a normal fowl

The effects of *castration* on bodily vigor lend themselves to objective experimental investigation By an adaptation of the old fashioned squirrel cage the spontaneous activity of a rat can be rather definitely determined Attached to the revolving



Graph showing the effect of castration on activity of rats

cage is a small housing compartment in which the animal sleeps and takes his nourishment But at will he can step into the wheel for amusement and exercise By a simple mechanical device each revolution of the wheel is recorded In this situation normal young adult rats will sometimes run as much as ten miles a day If, however, the testes are removed the activity is strikingly reduced

The results of such an experiment are epitomized in the accompanying graph The solid line represents the average activity of sixteen normal animals over eleven periods of ten days each The activity is indicated by the number of revolutions of the wheel Each revolution represents about one yard

of "progress" The broken line shows the degree of activity of sixteen rats of similar age from which the testes were removed on the tenth day of the experiment On the sixtieth day, when vigor was at its height, the normal animals were about four times as active as their castrated brothers Ultimately, as age crept on, even the normal animals showed a growing sedateness, but at the end of the experiment they were twice as energetic as the experimental group

So much for the effects of early castration In principle, the effects of *late castration* are similar, but because of the fact that adult development has already taken place, the details are somewhat different In the human species such emasculation sometimes results from accident, or it may be deliberately produced because of tuberculosis or other disease of the testes Rather soon after the operation the hair of the beard becomes so sparse that shaving is almost unnecessary The body hair largely disappears, the pubic hair pattern is transformed from that of the male to the transverse distribution of the female Obesity commonly follows The fat is characteristically localized around the hips and lower abdomen, the breast region, and the face The upper eyelids tend to become especially infiltrated, giving the subject a sleepy appearance The sexual impulse as well as potency either disappears completely or tends to marked diminution The reproductive structures other than the testes show varying, though commonly considerable, degrees of atrophy The voice in some cases in a measure regains the high pitch of youth Indeed, it is suggested that the shrill voice of age may be produced by the ebbing of the testicular hormone The skin of the eunuch becomes prematurely wrinkled The general appearance and demeanor resemble those of a fat, tired old man

TESTICULAR HORMONES—ANDROGENS

As mentioned in the introductory chapter, the use of gonad materials to stimulate the sex function dates back to the earliest

period of recorded history Endocrinology as a science got its first impetus from the work of Berthold who showed, in 1849, that testicular grafts permitted the normal masculine development of castrated cocks It was forty years later that the impetus was greatly augmented by the sensational report of Brown-Sequard upon the beneficial effects of testicular extracts in himself

The history of male sex hormone research from the time of Brown-Sequard has been a devious story marked by many difficulties, false hopes, and disappointments Sometimes the border line between credulity and charlatanry has been extremely vague Many kinds of extracts of many kinds of animals have been injected into many kinds of subjects, human and otherwise The glowing accounts of Brown Sequard have often been duplicated by enthusiastic recipients of gland extracts or their crude equivalents, gland grafts, but mostly these reports have failed to pass the scrutiny of critical realists Despite the admonition against putting "new wine into old bottles," the search for an endocrine fountain of youth has continued from that day to this

One typical instance of the quest has probably not hitherto appeared in print Shortly after the publication of Brown Sequard's famous report, the good news came to the ears of the inmates of an old men's home The young attending physician lent a willing ear to their request that they be given some of the wonderful new elixir He obtained some fresh sex gland material from a near by farmer and made a glycerine extract of it The first ten men to whom the material was given experienced a marvelous rejuvenation Eyes brightened, canes were laid aside, and chores were done with a new alacrity With credible scientific acumen, in the next ten cases the physician substituted blank injections of salt water The effects were no less happy than before—and no less transient

The story of gland grafting has been much the same as that of gland extracts Many temporary triumphs of suggestion have soon faded into disappointment In some cases, however,

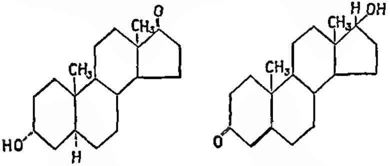
genuine success has been achieved—especially in animals Sand, for example, has recorded the instance of a decrepit old hunting dog that, after the reception of a testis graft, was remarkably invigorated He resumed as his favorite pastime an old habit of accompanying his master on bicycle rides Another striking example is that of an aged cat which developed a new set of teeth after this procedure

Among the first to secure objective and trustworthy results from testis extracts was Pezard (1918), who succeeded in bringing about almost normal development of the comb of a capon by the injection of saline extracts of swine testis Subsequently, the work has been confirmed with extracts of glands of several other animals and, more recently, with extracts from urine of men and women as well as of the blood of bulls and goats

The first significant step toward the isolation of the active principle of testis extracts was taken by McGee (1927), working in Koch's laboratory and using lipoid extractives of fresh bull testes The method, as subsequently improved by Gallagher and Koch, was to treat the tissue with strong alcohol, then take up the extract in benzene After evaporation, the material was next extracted with acetone, this, in turn, was evaporated and the residue dissolved in oil for injection By further purification with alcohol and sodium hydroxide solution, an ether extract was secured which was so potent that it sensibly influenced the capon comb in dosage as small as one one hundredth milligram That is to say, one gram would suffice to produce an effect in sixty five hundred subjects The active material when finally obtained in crystalline form was found to have the formula $C_{19}H_{28}O_2$ It was named *testosterone* The yield of this substance is only about two or three grams per ton of fresh gland material

Shortly after the successful work of McGee, it was discovered by Funk and collaborators that similar active material can be obtained from human urine Various procedures are used for preparing it, but the most common is to boil the fluid

for fifteen minutes after mild acidification, then treat it in a continuous extractor with benzene into which the active substance selectively dissolves Several chemists have succeeded in sufficiently purifying the material to obtain it in crystalline form Butenandt estimated from his own results that ten million gallons of urine would yield about five grams—the weight of a five-cent piece It was found to be a ketone alcohol derivative having the formula $C_{19}H_{30}O_2$ It is known as *androsterone* Like testosterone, androsterone falls in the same group



Androsterone *Testosterone*

of phenanthrene cyclo pentane steroids as do the female hormone *estrone* and the *adrenal* derivative *adrenosterone* Another active urinary product is *dehydroandrosterone* Both androsterone and dehydroandrosterone have been made artificially by Ruzicka, starting from the common substance cholesterol The most active material so far isolated is testosterone, which is six times as potent as androsterone The potency can be further enhanced by combining the testosterone to form acid esters such as the propionate, which is the material most commonly used in medical practice It is now made synthetically In addition to the three androgens above mentioned, approximately thirty similar derivatives have been prepared synthetically by chemical manipulation of sterols, but they have little or no physiological effect

In precisely what form natural androgen is secreted is not

known, but the general supposition is that it is as testosterone The evidence now available indicates that only a small amount is produced in the earlier years At about the time of puberty, however, the output markedly increases, reaching from forty to one hundred "International Units" in twenty four hours as compared with only a few units in childhood The amount falls off somewhat in the senile period It is a seeming biological paradox that nearly as much androgen is found in the urine of females as in that of males of comparable age Although the human material is a fairly rich source, the urine of such animals as have been studied yields but little androgen

There are several biological tests that can be utilized for the detection and *assay* of androgens The most frequently used are the comb of the capon and the seminal vesicles and prostates of castrated rats or mice Any of these structures react to the androgens however they are introduced into the body, but the strongest reaction is obtained when they are applied locally In the comb test they can be injected into the structure or applied to the surface Chemical colorometric methods are also more or less successfully employed One element conducive to uncertainty as to the biological status of these various androgens is the fact that different test objects fail to give comparable results Thus, androsterone, though less potent by the comb-growth test, is more effective in the restoration of the atrophic prostate Another puzzling fact is that extracts of urine are more potent than their content of known androgens would imply It is, therefore, assumed that the urine contains activating agents What these may be is unknown, but it has been found empirically that the potency can be enhanced by fatty acids and by an extract obtainable from adrenal glands

The effects of the androgens are most conspicuous in the secondary sex structures Their influence on the spermatogenic tissue seems to vary with conditions In appropriate dosage range there is some evidence that sperm production is increased, but when larger amounts are given—or moderate

amounts over too long a period—regression of the seminiferous tissue occurs with, sometimes, reduction of the sperm-cell count almost to zero This latter effect is probably due to depression of *gonadotropin* formation in the anterior pituitary, as suggested by Moore In females, the androgens have both feminizing and masculinizing effects In rats, testosterone produces luteinization in the ovary and androsterone brings spayed females into heat (estrus) In monkeys, testosterone in larger dosages leads to luteinization and inhibition of follicular development in the ovaries and, therefore, cessation of menstruation Similarly, excessive menstrual flow in women can be checked by injections of testosterone It is also useful in the treatment of the symptoms of the menopause If it is given in excess, however, these beneficial influences are marred by attendant masculinizing effects, such as hypertrophy of the clitoris and the growth of hair on the face

CLINICAL CONSIDERATIONS

Aberrations of androgen formation may take place in either direction, leading on the one hand to *hypergenitalism* or on the other to *hypogenitalism* The fact that any given gland can manifest a condition of underfunction—as the testis demonstrably does—establishes a high probability that it can likewise become overactive Thus, in case of the thyroid gland, we have both myxedema and exophthalmic goiter Similarly, the pituitary can give rise to either dwarfism or gigantism When we come to deal with the testis, however, our information on the subject of hyperactivity, i e, hypergenitalism, is curiously deficient so far as *adult* years are concerned Two facts render judgment difficult Standards of normality in the sexual field are not well established Furthermore, the data necessary to determine the degree of functional activity are of an intimate sort, bound up with emotional considerations Clean-cut, reliable statements are correspondingly difficult to secure There is a condition known clinically as *satyriasis*, in which, as

the name implies, eroticism goes to inordinate lengths Whether this is due, however, to endocrine factors, to nervous abnormality, or to social conditioning has not been satisfactorily determined A rare case of apparently true hypergenitalism in a human adult—apparently the first reported—was described by Fancher in 1936 When one testis was removed the patient's sex urge was reduced to manageable levels The literature also includes a considerable number of cases of malignant tumors of the testicles in which excessive output of hormones in the urine has been detected, but in these cases functional masculinity has not been conspicuous

When we come to deal with *prepuberal* conditions the case is much clearer Precocious sexual development in children represents, of course, for the age of incidence, a condition of true hypergenitalism In a classical monograph by Neurath published in 1909 there were collected the histories of forty three cases of *precocious maturity* in boys This was marked by excessive development of the genital organs, early deepening of the voice, and excessive growth of the body in general Many similar cases have since been reported Usually, however, the primary disturbance is in the anterior pituitary, the adrenal cortex, or the pineal gland Further details may be found in the chapters devoted to those structures In a small minority of the reported cases the cause of the precocious development has been found in the testes themselves

In some instances the precocity is manifested in the mental as well as the physical sphere, though commonly the subject gives a superficial impression of being more than usually childish because attention is fixed upon his size rather than his actual age The growth of the skeleton is at first stimulated and the child may give the impression of being well on his way toward gigantism Within a few years at most, however, the testicular hormone exerts its well known influence of stopping activity in the growth zones of the long bones, hence the ultimate stature is no greater than that of the normal adult if, indeed, a certain degree of dwarfism is not induced Particularly

significant in the diagnosis of the condition is what is known as the *bone age* of the subject The bones of the wrist lend themselves particularly well to the determination of the existing degree of physiologic maturity that obtains at any given time Like those of the skeleton generally, the wrist bones are first laid down in cartilage and later transformed into the final dense condition by the incorporation of mineral salts The deposition takes place from so-called *ossification centers* which appear in a definite succession correlated with the age As seen under the X rays, therefore, the number and size of the ossification centers serve admirably to fix the physiological as contrasted with the chronological age Todd refers to the skeleton in this relationship as "the physiological time clock"

Early hypergenitalism presents, at best, a difficult psychological problem The combination of the sex drive of an adult with the experience and judgment of a child is obviously dangerous either to the subject himself or to his companions The possession of unusual physical strength adds to the hazard The topic need not be elaborated

A frequently cited case of primary hypergenitalism is that of Sacchi, which was reported in 1895 At the age of nine the boy was generally overdeveloped and had large genitalia and whiskers He was discovered to have a malignant tumor of the left testis When the diseased organ was removed the normal conditions of childhood were in a considerable measure restored The abnormal hair of the beard and extremities fell out The penis became smaller and sexual activity ceased The voice, which had become like that of an adult, again attained the childish pitch

From the fact that the gonads of each sex contain in rudimentary form the structures of the opposite sex, it might be supposed that occasionally both sets would develop spontaneously—as they actually do—to give rise to frank *bisexuality* or *hermaphroditism*

Somewhat similar in the incongruous end results is the condition of *sex reversal* in which masculinity is superimposed

upon initial bodily femininity Such a condition can be set up experimentally with no great difficulty, the method in general being to start with one sex and by appropriate surgical manipulation bring about reversal to the intergrade condition Among the experiments to this end were those of Steinach in 1912 He removed the ovaries from female guinea pigs and replaced them with the sex glands of their twin brothers These brevet males thereupon outgrew their female controls and showed the skeletal characteristics, the coarser hair growth, and the pugnacity of normal males *Numerous other examples of sex transformation resulting from testis grafts could be cited.*

Another method of setting up sex reversal is, by surgical operation, to attach tadpoles side by side in parabiosis Witschi, in such experiments, obtained pairs in which the male was normal and the female had gonads ranging from a slightly modified ovary to a typical testis Artificial hermaphrodites among higher forms can be obtained by grafting testes into females or ovaries into males

Hamilton and Gardner have shown that the injection of pregnant rats with androgens leads to a condition of *pseudohermaphroditism* in the female offspring, the ovaries being depressed and the male secondary sexual structures being stimulated What might be called consecutive hermaphroditism is occasionally seen in birds in which the male rudiments of the female gonads sometimes develop into functional testes Previous mention was made of certain tumors in women, *arrhenoblastomata,* which secrete androgen and bring about marked degrees of masculinization In that normal men and women excrete both estrogens and androgens it would seem that a substantial degree of hermaphroditism is actually the common condition

A considerable number of the cases of bisexualism in higher animals have been reported The condition in man is rare, but Goldzieher, in 1939, found records of twenty cases in which the condition had been verified by microscopic examination *A considerable number of unverified cases have*

also been reported In Sinigaglia's (1919) case the individual was twenty-eight years old and was married The external genital structures were female In a scrotumlike sac within the left labium, operation disclosed a testis and, from this, seminal fluid containing spermatozoa was secreted The right gonad consisted of mature ovarian and some rudimentary testicular tissue In another case, reported in 1920, a "man" of twenty-eight years was found at operation to have a uterus of normal size and with two normal fallopian tubes On each side within the abdominal cavity occurred a mixed sex gland containing both ovarian and testicular parts The ovarian portions contained follicles, some of which were apparently fully developed, and the testicular portions showed well-developed male sex cells In only three of the twenty known cases was there found a discrete testis on one side and an ovary on the other, in the remaining cases the glands were mixed

A common functional, intergrade sexual condition is that known as *homosexuality* It is a truism of psychopathology that all men have feminine traits and all women masculine propensities Indeed, all temperamental gradations from complete masculinity to complete feminity may be seen The term "homosexuality" is conventionally applied, however, only to those cases in which structural males are outspokenly feminine in psychological or social reactions and vice versa The condition is fairly common and is the source of many tragedies Few maladjustments are so subtly demoralizing as is the possession of ardent erotic impulses which can be satisfied only with individuals of the same sex. Society attaches high culpability to the condition and stigmatizes the subjects as perverts The psychologically sophisticated recognize in the strong disapprobation that is visited upon the victims an unconscious revelation, often, of repressed homosexuality in the critics Some of the results of homosexuality are lack of a sense of security and social status and, in the more extreme cases, a psychotic adjustment to life

The extent to which clinical homosexuality is due to hor

monal factors and the extent to which it is due to social conditioning is not adequately known The psychoanalytic school attach predominant importance to early experiences They stress, especially, failure of emancipation from attachment to parents and failure to complete the emotional evolution of puberty as the chief causes Other students, who are more organically minded, seek for physiological explanations of the disorder In many instances of homosexuality bodily indicators of aberrant hormonal influences are entirely lacking In a substantial proportion of the cases, however, dysplastic features in bodily make up have been found In males, these include sparseness of beard, relatively broad hips, and feminine distribution of the pubic hair Many studies have been made of the androgen and estrogen output in the urine of homosexuals In a considerable proportion of the cases in males an abnormally high estrogen to androgen ratio has been reported, but the day to-day and subject to subject variations in output are so great as to cast doubt upon the statistical validity of the findings Rarely, partial or complete correction of the homosexuality in males has been reported following the implantation of testicular grafts, but usually the results of this procedure have been negative Similarly, with such active agents and such methods of utilizing them as have yet been discovered, injections of sex hormones have given but meager returns

When we turn to conditions of *clinical hypogonadism*, the pictures become much clearer In a previous section the general effects of androgen deficiency were noted Complete hypogonadism results either when the testes are destroyed by disease or when they are removed surgically or by accident The condition is known technically as *eunuchism* or *genital infantilism* Although, as previously stated, failure of descent of the testes in some cases may not interfere with hormone production, in other cases this condition, too, so interferes with development as to result in a condition quite like that of prepuberal castration

A characteristic case of eunuchism has been described by Lisser The patient was first seen eleven years after an injury

that had resulted in marked atrophy of the gonads He was then thirty-one years of age He was of the "thin type" rather than the more common obese variety He presented an asthenic, emaciated appearance with notably poor posture "He was a weak, whiny sort of person, economically a failure, depressed and melancholy He was physically feeble and sluggish " The blood pressure was about twenty points below normal and he was anemic. The chest, arms, and legs were devoid of hair, and pubic and axillary hair was deficient Instead of shaving daily, as had been his wont before the injury, once a week sufficed The skin was wrinkled and showed poor vitality General inefficiency in the sexual sphere was reported

The *psychological effect* of castration varies rather markedly in individual cases If the defect arises in early childhood, normal male aggressiveness fails to develop If, however, the defect does not become operative until the puberal changes have become in a measure established, a certain part of the masculinization may persist throughout life

The *treatment* of eunuchism is, of course, to supply artificially the missing androgenic hormone In the years prior to the advent of purified androgens, recourse was had to crude testicular extracts or to gland grafts In view of the fact that the yield of androgens from testicular tissue even with the best of modern technics is extremely small, it is a matter of no surprise now that clinical results with the earlier extracts were practically negligible except as they contributed to unwitting psychotherapy The case for gland grafts was somewhat, though not greatly, better When gland tissue from the lower animals was employed, it soon degenerated and was cast off In certain cases, when higher apes were used as donors, somewhat better results have been reported Even when human tissue has been utilized only occasionally has the outcome been convincingly favorable—psychotherapy aside There are, however, on record a few instances of objective results to supplement the large number of cases of subjective improvement For example, Lisser has recorded an instance in which one

gonad was removed from a young man for the correction of excessive sexual vigor and transplanted into a man fifty years of age The recipient had always been beardless, his voice was high pitched and he had had no experience of sexual desire or activity Within three months after the operation he was able, he stated, to experience successful sexual activity for the first time in his life Whether or not this was mere boasting, he at any rate developed a beard and increased body hair growth A second case was that of a patient who suffered an accident in his twentieth year resulting in complete testicular atrophy The nails of his fingers and toes became very rough and piled up in ridges Following implantation of testicular substance from a ram, the nails became normal and smooth Another instance of objective evidence of the efficacy of this procedure is that of a man whose sparse gray hair regained its normal, earlier brown color and grew more profusely after an implantation Cases like the foregoing, though somewhat rare serve to substantiate the fact that the testicular hormone is able, under favorable conditions, to bring about unquestionable physical as well as psychological changes in man as well as in the lower animals. There is some evidence that better results accrue when both the donor and the recipient of the graft belong to the same blood group

With the advent of testosterone propionate, the treatment of eunuchism has become substantially more hopeful The dosage that is needed varies somewhat from case to case Two or three injections a week of twenty five milligrams each may suffice, but Thompson believes that, generally speaking, as much as fifty to one hundred milligrams daily is desirable Soon after the injections are started the secondary sex characteristics of the adult male gradually begin to appear The infantile penis may reach normal size, the prostate develops and masculine hair growth appears in the pubic and axillary regions, on the face and the body The pitch of the voice rapidly assumes the characteristic masculine quality According to Thompson, erections and seminal emissions become frequent and even pri

apism may result A marked increase in appetite and body weight (up to forty pounds in four months) is seen The patients do not become obese but show gratifying and even dramatic increase in the size, firmness, and strength of the muscles The basal metabolic rate is increased, in some patients as much as thirty points Augmentation of vigor and sense of well being are characteristic The subjects become capable of, and have the initiative to do, much more work, both mental and physical Their interest and proficiency in games that involve muscular co-ordination and physical stamina increase Finally, to be emphasized is the loss of effeminate characteristics Whereas before treatment the patients tend to run away from arguments and physical combat, after treatment they often welcome opportunities to demonstrate their prowess

Less in degree, but *similar in kind*, is the condition of partial androgen deficiency known as *eunuchoidism* The term *sexual infantilism* is applied to this group as well as to the true eunuchs The common cause of the condition is failure of the anterior pituitary to produce a sufficient amount of gonadotropic hormone The manifestations of eunuchoidism vary rather widely in accordance with the degree and time of onset of the hormonal deficit In the milder cases, in which the testes are only moderately below par, the patients are usually of medium height although their proportions, according to Goldzieher, are always typically eunuchoidal That is, the span of the outstretched arms from finger tips to finger tips exceeds the total height and the upper part of the body is shorter than the lower The most notable skeletal abnormality is a characteristic development of the hands and feet the fingers and toes are unusually long and slender Genital development in the milder cases may slowly progress to a stage that permits some degree of regular sexual activity The sex organs proper may attain almost normal size and the secondary sex characteristics, hirsute and otherwise, may be approximately normal The functional deficiencies of the milder degrees of eunuchoidism include low or absent fertility, sparseness or complete lack

of sperm cell formation, and lack or weakness of sexual urge and potency The patients are commonly of the lean, asthenic type, are high strung and oversensitive These various manifestations of the milder cases progressively graduate with higher degrees of androgen deficiency into the manifestations of complete eunuchism

The *treatment* of the condition depends upon its cause When the pituitary is at fault, attempts may be made to stimulate the testes by injections of extracts containing the gonadotropic principles of that gland Alternatively, gonadotropins from other sources, such as the urine of pregnant women or the blood of pregnant mares, may be used Should these measures be unavailing, the next recourse is to androgen itself Testosterone propionate in oil may be injected intramuscularly or occasional implants of testosterone tablets may be placed beneath the skin The frequency with which the implants need replacement is not yet clearly defined, but success has been reported in some cases when one hundred and fifty milligrams of the substance has been used each two or three months Because of the depressing effect of androgens upon the anterior lobe of the pituitary, such treatment is theoretically contraindicated when the initial condition is deficiency of that structure Practically, however, this consideration may be waived According to Turner's findings, testosterone in smaller dosage stimulates the testicular function itself, as shown by improvement in the sperm count But larger doses have often been noted to cause at least temporary depression in the sex glands

The infantilism that accompanies Frohlich's disease, as described in a previous chapter, presents essentially the same clinical problems as does the type of eunuchoidism discussed in the preceding paragraphs

One of the more common abnormalities in the sex field of males is, as previously noted, *failure of descent* of the testes from the abdominal cavity into the scrotum (*cryptorchidism*) It exists in varying degrees in different subjects In some cases both the glands remain completely inside the abdomen Some

times one descends and the other remains within, and finally one or both may achieve only partial descent, being retained in the inguinal canals in the groins In some cases cryptorchidism has no significant influence upon androgen production, the subjects attaining to full masculine status In such instances the cells of Leydig are found to be approximately normal At the other extreme, a condition clinically indistinguishable from complete eunuchism may be found Curiously, the condition of cryptorchidism may present a genuine problem in diagnosis One of the normal reflexes of the body is a retraction of the testes under certain cases of special stimulation When descent has not fully taken place, the gonads under the excitement of a physical examination may retreat so high into the inguinal canals as to be overlooked In such cases when relaxation is secured by putting the patient into a warm bath the glands may sufficiently descend to be recognized

The *treatment* of cryptorchidism is, first, to attempt to bring about the completion of the developmental maneuver by the use of stimulating hormones Success has often been achieved from the use of various gonadotropins as well as testosterone propionate Should these measures fail, surgical intervention is indicated, either to correct or to forestall the condition of infantilism and to obviate the danger of malignant tumor formation in the retained glands

In numerous of the conditions described in the foregoing paragraphs the condition of partial or complete *sterility* exists It may be found also in other cases in which no objective evidence of testicular deficiency is perceptible Microscopic examination of the seminal fluid, however, may show scarcity or absence of sperm cells or poor motility of such as are present Prevalence of abnormal forms is also frequently noted The condition may arise from thyroid or from pituitary deficiency or it may be due, apparently, to primary functional inadequacy of the gonads themselves The treatment depends upon the cause In some cases the use of desiccated thyroid, and in others gonadotropins, has been followed by restored fertility Occa

sionally, testosterone in the lower dosage range may be helpful but usually, and especially in the larger dosages, its use has not been successful

Whether men normally experience anything comparable to the condition of the menopause in women is a question upon which physicians are not agreed There is certainly no definite period of loss of sexual function in the male comparable to that in the female Nevertheless, there does occur more or less waning of sexual activity with advancing years and this condition, when associated with loss of vigor and of temperamental equanimity, is sometimes spoken of as the *male climacteric* Its age of onset varies widely from one man to another Engle states, however, that more than half of all men over seventy years of age still show active sperm-cell production In some instances considerable improvement in spirits and bodily vigor has been noted in such cases following the use of testosterone, but its actual value and the details of treatment remain to be determined in adequate numbers to permit final judgment

A condition finally to be mentioned, in many instances of which deficiency of androgen output plays a causal role, is that of *impotence* In many cases of organic eunuchoidism, impotence is a symptom which is corrected by any treatment which ameliorates the cause Often, however, the condition is partly or wholly of psychic origin and can often be corrected by psychotherapy

THE CONTROL OF THE TESTES

Most of what is known as to the control of testicular functions has been included in the foregoing discussion The fact that the glands are well supplied with nerves would suggest that they may be under central *nervous control* The occasional persistence of gland grafts in a functional state, however, indicates that in this case, as in that of other glands, such control is not essential to their function Whether any nervous control of secretory functions is exerted is not evident

Directly or indirectly, the testes are influenced by various of

the other endocrine glands As noted earlier, adequate functioning of the *thyroid* is a necessary condition for the normal development and activity of the gonads In childhood myxedema, underdevelopment of the testes and failure of sperm-cell formation is a common condition The same thing is seen in experimental thyroid deficiency in animals Myxedema arising later in life also leads to regression in the sex field McCullagh has reported an instance of testicular hypofunction in a man who failed to respond satisfactorily to testosterone Under thyroid treatment he speedily normalized

On the basis of present knowledge, it appears that the dominant controlling mechanism for the testis is the *anterior lobe* of the *pituitary gland* As previously stated, removal of this structure in young animals results in failure of sexual development Implantation of anterior lobe grafts permits normal development The same relationship is also seen in older animals Greep and Fevold (1937) have reported particularly enlightening experiments on the pituitary testicular interrelationship They found that in animals deprived of their hypophyses sperm-cell formation could be maintained by injections of pure follicle-stimulating pituitary extract Nevertheless, atrophy of the Leydig cells and corresponding regression of the accessory genital structures took place When luteinizing extract was given, however, the atrophic interstitial cells were restored and resumed secretion of male sex hormone, as was indicated by the regeneration of the accessory structures In women, the gonad pituitary relationship results in cyclic sex behavior Whether a similar relationship holds in the other sex is not clearly known, but the bulk of the evidence is of negative tenor However, in men there is some evidence of cyclic waxing and waning of the sex impulse and this, to whatever extent it actually occurs, is probably due to the antecedent tides in the secretion of pituitary gonadotropin

The case for the *adrenals* in relation to testicular functioning is quite similar to that for the thyroid Adrenalectomy causes cessation of sperm-cell production as well as testicular

atrophy Conversely, there is some evidence that administration of cortical extract causes hypertrophy of the testes More convincing is the clinical evidence discussed in a previous section If adrenal hyperactivity occurs during childhood, sexual development may be markedly accentuated, leading to precocious puberty When the condition arises in later years, adrenal virilism is often seen Ehrenstein and Britton have reported also that cortical extracts contain an activating principle which increases the potency of androgens

As will be noted later, some cases of *pineal gland* tumor are associated with precocious puberty, which fact has often been interpreted as indicating a controlling influence emanating from that structure

Rarely, tumors of the thymus gland have been found in association with hypergenitalism Whether this fact indicates, however, that the thymus exercises any regular control over the gonads is doubtful Removal of the thymus commonly results in no perturbation of the sexual function.

PSYCHOLOGICAL CONSIDERATIONS

That the sex hormones have important influences upon *temperament* and *emotional development* is commonplace knowledge By castration the fiery bull is converted into the docile ox The induction of masculine temperament in spayed females, as demonstrated by Steinach in guinea pigs, has often been confirmed in other animals Domm's experiments on chickens are especially enlightening in this connection When the ovaries are destroyed, leaving rudimentary gonadal rests, regeneration of either ovary or testis may take place The result is that the temperament of either hens or cocks develops in accordance with the nature of the regenerated structure Conversely, by the use of appropriate extracts baby chicks can be made to crow with canarylike squeaks and to attempt mating behavior before they have shed their down Such evidences from animal experimentation could be multiplied at great

length There is no question, then, that fundamentally the temperament is largely determined by gonadal factors

McCartney has reported a study of the psychology of human castrates as seen in a group of twenty three subjects in China These included twenty Chinese eunuchs, abandoned after the dissolution of the Imperial Court in Peking, and three Russian refugees In addition to the well known physical defects which follow the operation, the subjects all showed mental abnormality They were highly introspective in temperament They could talk intelligently but never volunteered information and gave the superficial impression of stupidity They were methodical in their actions but only two showed any genuine evidence of purposefulness Their emotional reactions were defective They were cold and passive in the face of dire poverty Two had been sentenced for murder and half the group had otherwise been in trouble because of indulgence in ugly temper All appeared to be moody A considerable number claimed to have continued sexual intercourse and all said that they indulged in homosexual practices and other perversions

Other observers have noted instances in which castration produced much less effect than in McCartney's cases Rowe has cited the instance of a truck driver who was vigorous physically and well adjusted mentally He was able even to maintain a fair degree of normality in his marital life Such cases raise the question to what extent the effects of castration in adult years are actually due to deprivation of gonad hormones and how much to the operation of social forces The emasculation would presumably serve to induce a strong feeling of inferiority and this would be reinforced, consciously and unconsciously, by a variety of suggestions received in daily contacts with people to whom the eunuch is an object of contempt.

Castration in childhood leads to a failure of the emotional maturing that normally occurs in adolescent years To the eunuch or eunuchoid all romance is denied and only platonic social relationships are possible The psychology of sex is a

theme too broad to be treated in detail in a work of this sort Fraser, Havelock Ellis, and many other writers have dealt with the subject at great length

Directly or indirectly, the gonad hormones serve as the dominant theme in much of the world's best—and worst—literature The contrast between a *virile*, dominating personality and that of a weak, whining *emasculate* is all illuminating The impulse to romance is but a slightly disguised aspect of the mating instinct The rich emotional life centering in the home, when homemaking is successful, and the manifold disharmonies, when it is not, all have their source directly or indirectly in the sex instincts These, in turn, are dependent upon the sex hormones With this element eliminated from life, little of romance would be left A clear eyed recognition of this fact detracts no whit from the wonder of it The *Mona Lisa* is nonetheless beautiful to one who happens to know the chemistry of pigments

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VII. THE FEMALE SEX GLANDS—THE OVARIES

THE ANATOMY OF THE OVARIES

The ovaries in the adult woman, as seen in the gross, are a pair of bean shaped organs about an inch and a half long and an inch wide Each is supported in a sheet of peritoneum covered tissue lying beneath the fallopian tubes in the upper segment of the pelvis In childhood the surface of the gland is white and smooth, but after puberty it takes on a somewhat roughened appearance due to the scars which form after the discharge of the sex cells

Each ovary consists of an outer *cortical portion* made up of a supporting connective tissue in which are embedded the *follicles* in which the egg cells, the *ova*, develop Within the cortex is the *medullary portion* which is composed of connective tissue, lymph capillaries, blood vessels, and rather sparse strands of smooth muscle and elastic tissue fibers The *blood supply* is derived from the uterine and ovarian arteries These, after a somewhat tortuous course, penetrate to form a plexus in the medulla of the gland From the plexus smaller branches run out into the cortex, branching to form capillaries The *veins* are rather large and tortuous in the medulla, finally coming together to form the venus plexus. The ovaries are *innervated* by the ovarian and uterine nerves There is some evidence that these are accompanied by sympathetic branches

The ovary, like the testis, takes *embryological origin* as the *genital ridge*, one on each side, at the back of the body cavity During the earlier weeks it cannot be distinguished from the early

testis, the description of which, in the preceding chapter, is equally applicable to the female gland. Its unique tissue, the *germinal epithelium*, made up of the cells which later give rise to the ova, can be recognized under the microscope, however, as early as the sixth week of life. As in the male, the sex elements are carried from generation to generation without ever having been a part of the body tissues proper.

The methods whereby the formed ovary is evolved from the early cell mass are highly complex. In general, the process involves the formation of a supporting structure in which the sex cells are contained and in which they multiply. The individual sex cells, the ova, are first set off in spherical or cordlike masses, the *sex cords*, which permeate the supporting tissue, the stroma The sex cords then divide into smaller masses to form the *graafian follicles*. For further details of fetal development textbooks of embryology may be consulted

Consideration may now be turned to the microscopic structure of the finished gland. *Histologically*, it is seen to be covered by a thin layer of peritoneal membrane which is an extension of that lining the body cavity Beneath this layer lies the germinal epithelium, which spreads out to surround the contents of the organ Immediately underneath the germinal epithelium lies a dense layer of connective tissue, the *tunica albuginea* Within the cortex are embedded the characteristic ovarian elements, the *follicles*, in which the germ cells proper mature. The fluid within the follicles is a rich source of sex hormone.

At birth the number of follicles is very large, but they gradually diminish in number up to the age of puberty—though at that time they are still numbered in thousands. Only a small proportion of the original follicles ever reach the final stage of fully matured ova—approximately one in a hundred. The remainder undergo a regressive change, *atresia*, until at the time of the menopause very nearly all of the follicles have finally disappeared.

When the girl reaches the age of puberty, a new structure

makes its appearance in the ovary One of the graafian follicles lying near the surface of the organ becomes distended with follicular fluid Instead of then regressing to be absorbed within the gland, the follicle ruptures and the ovum and the surrounding follicular fluid are set free in the body cavity The sex cell then makes its way into the uterus If it meets and fuses with a male germ cell *en passant*, the process of fertilization has occurred and pregnancy has begun The follicular fluid discharged with the ovum has provided the potential mother with a supply of a hormone which sets up various changes in the organism looking toward the sustenance of the newly formed embryo Should this first possibility of reproduction not be realized, however, as it commonly is not, the whole effort comes to naught and the uterus is cleared out for its next occupant The girl thus experiences her first menstrual period

Such frustration, however, is not nature's fundamental purpose and the ovary proceeds as though pregnancy were to ensue In the ruptured graafian follicle from which the ovum is discharged, certain of the remaining cells rapidly undergo multiplication Each becomes filled with a peculiar, fatlike substance of characteristic yellow color, forming the so-called *luteal cells* The luteal cell mass becomes completely surrounded by a supporting membrane into which blood capillaries make their way, thus providing for the nourishment of the new structure The process of cell multiplication continues until finally a discrete, organized functional unit is evolved This, because of the color of its constituent cells, is known as the *corpus luteum* (yellow body) It projects from the surface of the ovary like a half-submerged, marrow fat pea

The further history of the corpus luteum depends upon whether or not pregnancy is achieved If nature is destined to charge off the transaction to profit and loss, the corpus luteum reaches its maximum development in about two weeks Then a process of absorption begins and in about two months nothing remains but a small scar in the surface of the ovary Should

pregnancy occur, the yellow body enlarges further and per sists in its fully developed stage for five or six months, con tinuing to produce its hormone during that period At this time it is a half inch or more in diameter During the last three months of pregnancy it gradually recedes, but at the end of that period it is still a fairly conspicuous structure

The woman during her reproductive age is not restricted entirely for a supply of follicular hormone to that periodically discharged from the ripened graafian follicles In addition to those destined to complete their normal evolution, a large num ber of follicles develop only to the point of forming their characteristic fluid and then gradually degenerate and are ab- sorbed

Further details of the reproductive processes will be given in a subsequent chapter

THE FUNCTIONS OF THE OVARY

The primary function of the ovary is, of course, to produce the germ cells by which the race is perpetuated Scarcely less important, however, is its secretion of regulatory hormones by which the pregnancy is initiated and brought to fruition At what stage the ovary first begins to function as an endocrine organ is not clear In the preceding chapter, evidence was cited that the testes begin to elaborate a hormone even during the fetal stage of development By analogy the ovaries, too, might be assumed to begin the processes of internal secretion at a similarly early stage The structural changes in the ovary before birth are such as to suggest the actual production of hormone, but these changes may merely foreshadow a later functional career To determine experimentally whether or not the ovary does give rise to an internal secretion in the prenatal months presents a difficult problem The entire fetus is exposed to the circulating hormones of the mother, hence, even were the gonad shown to contain an active principle, the finding would be ambiguous The hormone might have been

either produced in the ovary or taken up from the blood stream of the mother As a matter of fact, Frank, whose work in this field is outstanding, reports that he has found no greater amount of follicular hormone in the fetal ovaries than in any other part of the developing body He accordingly believes that the hormone is not produced prior to birth

Even during the stage from birth to puberty our knowledge of the endocrine significance of the ovary is scanty The little girl, like her brother, at this period is largely neutral as regards sex. But there are certain structural differences between the two that suggest a hormone influence Particularly, the shape of the pelvis, in its minor likeness to the adult female form, early foreshadows the function of childbearing Many observers believe, too, that little girls come early to differ in temperamental qualities, but to what extent the differences may arise through social conditioning is, as previously noted in case of the boy, hard to determine

On a priori grounds, there is no necessity for assuming the early operation of hormone factors because, as previously mentioned, it is known that the sex is primarily predetermined by the constitution of the fertilized ovum The sexual differences in the early years might thus logically be ascribed to genetic rather than hormone factors On the whole, however, as Evans states, the hypothesis that best serves to co-ordinate all the facts is that "the germ cells of the new individual, the sex of which has been determined by chromosome constitution, begin to affect the somatic (body) cells at a very early and certainly embryonic period, though the soma possesses certain inherent tendencies to express itself in a neutral, or asexual, form Could castration be carried out sufficiently early such a neutral form would always result, a single sex undifferentiated form which would be characteristic of the species"

With the onset of puberty, the picture becomes clear From this time on, it is certain that at least two internal secretions are produced, the follicular hormone and that of the corpus luteum The functions of each have been investigated, partly

by noting the effects of administering the hormones and partly by a study of the results when they are deficient

EFFECTS OF OVARIAN DEFICIENCY

Many sorts of animals have been deprived of their ovaries (*spayed*) in the early period of life before these organs normally assume the functions of reproduction The contrast later on between such animals and those allowed to develop with their full complement of hormones gives us a variety of important data regarding the part played by the gonads

The result of early spaying is closely comparable to that of destruction of the testes as described in the previous chapter In a word, the juvenile conditions persist throughout life, the subjects remaining sexually neutral The accessory genital structures fail to keep pace with the body growth The normal periodic attraction to and for the male (heat or *estrus*) completely fails to appear If the operation is delayed until after the puberal evolution is completed, the result is atrophy of the sexual organs and loss of the reproductive instincts

Little is known as to the effects of early destruction of the ovaries in the human species There is, however, a vagrant account often cited in textbooks of a statement ascribed to Roberts, who made a few observations in India He reported that young girls who have suffered this mishap become abnormally tall, a fact which implies that the growth zones in the long bones persist beyond their normal time of closure as they do in the castrated male The girls remain throughout life, as do spayed animals, in a sexually neutral condition The internal reproductive organs remain small External evidences of the ovarian hormone deficit are failure of development of the breasts and vulvar structures as well as of the axillary and pubic hair

In clinical practice, cases are occasionally seen of so-called female *eunuchoidism* (a misnomer), in which the subjects conform rather closely to the foregoing description The condition

usually arises from deficiency of secretion of pituitary hormones but may result from primary failure of the ovaries as a result of childhood injury or disease That deficiency in any other glands leads to this type of infantilism is possible but not proved Regardless of the primary cause, the symptoms are those of ovarian deficiency They are most obviously apparent in the skeletal abnormalities—the excessive height and abnormal span The failure of the epiphysial lines of the long bones to close at the puberal age is recognizable in X ray plates The pelvis is relatively narrow The face tends to be long and narrow and the chin pointed The palate is high arched The teeth are somewhat crowded and the upper lateral incisors often stunted The fingers and toes are long and slender Deficiency or delayed development of the secondary sex characteristics are important diagnostic features The breasts are undersized and may contain almost no glandular tissue The nipples are immature and are surrounded by small areolae In the less marked cases the breasts are cone shaped and pointed Pubic and axillary hair growth is retarded and scanty The vulva remains of the childish form The vagina is contracted and short The uterus retains its infantile size, shape, and position Usually the menstrual function is grossly abnormal Amenorrhea is common or the flow is scanty, irregular, and accompanied by pain Occasionally the only marked deviation from normality is dysmenorrhea The periods in any case are usually delayed—often to the fifteenth year or later Fertility is low or absent

Despite the genital inadequacy, the subjects may attain to a substantial degree of adult psychological normality They are often quite feminine in attitude and general appearance and may be genuinely and romantically interested in the opposite sex.

In contrast with the scantiness of the evidence regarding the results of ovarian deficiency induced in girlhood, we have an abundance of data regarding the effects of that condition when it occurs *after puberty* In surgical practice it unfortu

nately often becomes necessary to remove the sex glands because of disease Many accounts of the results have been published The effect, in general, is to bring on an artificial *menopause*, the condition that normally supervenes in women at the close of the reproductive period of life Menstruation ceases The uterus and the breasts undergo atrophy in greater or less degree Sterility, of course, ensues The subjects commonly increase in weight, the fat having a tendency to be laid down especially in the region of the hips Not infrequently, hair growth suggestive of that of the normal male appears on the face, though more than ovarian deficiency is required to produce the "bearded ladies" of the side shows The sympathetic nervous system goes through a stage of instability during which any slight stimulus brings about the disturbance known as "hot flashes" These may occur rather infrequently or many times a day The skin flushes and the subject experiences a distressing sense of heat Marked sensitivity to adrenin has been demonstrated, by this agent, hot flashes can be induced at will (Hannan)

Rowe and Lawrence have reported elaborate studies of the metabolic results of ovarian deficiency In the main, the abnormalities are not striking The most marked is about a 15 per cent reduction in the rate of oxygen consumption Associated with this, as would be expected, is a slight reduction in the body temperature and sometimes moderately low blood pressure Carbohydrate metabolism is also reported to be disturbed, as shown especially by the response to graded doses of the sugar, galactose In experimental animals, too, the effect of ovarian deficiency is a reduction in the metabolic rate Considerable variability is noted, but in general the magnitude of the effect is about the same as in the human species Surprisingly, in women the psychological effect of ovarian deficiency is not manifested particularly in the sex sphere Erotic desire often shows no diminution and, indeed, may be increased Rather, according to Rowe, deprivation of the ovarian hormones during the normal reproductive years results in a

peculiar quality of nervous tension and irritability. "An insistently expressed egoism is the keynote of the hypogonad character Coupled with, and dependent on, this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies Hyperemotionalism and self pity are united with an attitude of acid criticism of environmental conditions that are always unsatisfactory The psychological study of the average woman suffering from ovarian insufficiency would be a profitable though scarcely a pleasant task"

Complete destruction of the ovaries deprives the subject of both the follicular and the corpus-luteum hormones The results of the operation are, therefore, ambiguous as related to either hormone individually The differential effects are best studied by removal of the corpora lutea, leaving the follicular apparatus intact—an operation that is not difficult to perform In experimental animals, the most striking outcome is an interference with the processes of pregnancy If the operation is performed early after fertilization of the ovum, the uterus quickly loses its receptivity and the beginning embryo passes through the organ without gaining a foothold Technically stated, the function of *nidation* ("nesting") is lost If time is allowed for nidation to occur before the corpus luteum is removed, the preparations for the further entertainment of the newly generated being quickly come to an end and abortion follows It will be appreciated that this early abortion is somewhat similar to the normal process of menstruation, which also is accompanied by a suddenly developing lack of the corpus luteum hormone

In the human species, destruction of the corpus luteum very early in pregnancy seems not to have been reported If the operation is performed—as it has been—after the pregnancy has persisted a month or two, the gestation proceeds in its normal course Neither the mother nor the child suffers apparent harm From other types of evidence, however, it is sufficiently established that the secretion of the corpus luteum

does have a significant local effect on the uterus in the human as it does in other species, hence the generalization is warranted that an important function of the secretion is the preparation of the uterus for the reception and nourishment of the beginning embryo

In some of the lower forms, e g, the guinea pig, the mechanism for the reception of the fertilized ovum in the uterus has been clearly worked out A combination of two factors is operative The lining of the uterus is influenced by the corpus luteum hormone to undergo a wave of increased functional activity The inner layer becomes thickened, the mucous glands enlarge, and the blood supply increases If the sensitized structure is now stimulated mechanically to imitate the contact of the ovum, a local exaggeration of the processes just described takes place, known technically as the *decidual reaction* This is the normal way in which is begun the *placenta*, the organ through which the fetus maintains its vital relationships with the mother After the corpus luteum is destroyed, this decidual reaction can no longer be evoked

We have some evidence that a similar mechanism is operative in women Occasionally it happens that the fertilized ovum on its way to the uterus becomes fixed to the wall of the canal which leads to that organ, the *fallopian tube* Thus, a "tubal pregnancy" is set up Although the uterus is thereby spared its customary part in the processes of gestation, its lining nevertheless shows the normal, early reaction of pregnancy Since the local stimulating effect ordinarily exerted by the presence of the fetus is lacking to account for the reaction, it can fairly be ascribed to the influence of corpus luteum hormone

It will be recalled that, lacking fertilization of the ovum, the corpus luteum commonly soon regresses and is absorbed Occasionally, however, it persists in a more or less active functional state to form a so called *luteal cyst* This persistence of the structure has long been recognized in veterinary practice When it occurs, the animal no longer periodically ovu

lates or comes into "heat" The result is persistent sterility The condition is effectively treated by mechanical rupture of the luteal cyst, whereupon the sexual rhythm is resumed This experience of the veterinarians afforded, perhaps, our first evidence of an antagonism between the ovarian hormones The onset of heat, as will be discussed later, is a function of the follicular hormone

In ovarian deficiency the sex hormone content of the blood and the urine is depressed—roughly in accordance with the degree of the defect

Many additional details regarding the clinical consequences of inadequate ovarian hormone production can be found in technical treatises such as the books of Goldzieher and Hamblen cited at the end of this chapter

THE OVARIAN HORMONES

Not infrequently, experimental investigators and surgeons have reported the successful use of ovarian grafts to prevent the various effects that characteristically follow destruction of these organs The procedure has never been very satisfactory, however, in practical therapeutics because of a high percentage of failures to obtain "takes" The grafts commonly die and are absorbed Moreover, human patients have a well grounded reluctance to submit to surgical procedures

More commonly, therefore, recourse has been had to feeding or injecting preparations derived from the ovaries. Many enthusiastic accounts of substantial benefit have been reported It is noteworthy, however, that the better endowed the investigating clinician with critical scientific judgment, the poorer have been his reported results from ovarian feeding In experimental animals the results have been substantially nil More and more, therefore, has sound medical opinion crystallized to the effect that the benefits that follow such medication are but further examples of the proverbial success of psychotherapy Generally speaking, the results of injections

of ovarian preparations in the earlier period were quite as dubious as those from oral administration Two factors, as is now apparent, were operative in the generally negative results secured Even potent ovarian preparations are mostly ineffective when taken by mouth, either because of the destruction of the hormones by the digestive fluids or else because they are not absorbed in significant amounts The other factor is lack of potency in the preparations, however used Until recent accessions to knowledge of the hormones, the producers were necessarily working in the dark in their manufacturing operations Their ovarian preparations amounted merely, or mostly, to organic debris quite devoid of hormone content

A flood of new light suffused this dark corner of the endocrine field when Allen and Doisy, in 1923, succeeded in demonstrating that the follicular fluid of animals contains in potent form an effective stimulating substance This they assumed to represent a true ovarian hormone Although several previous observers had produced more or less active extracts, they had commonly used as experimental animals rabbits, which are somewhat inconstant in their sexual reactions Hence, the scientific world had remained rather skeptical On the other hand, Allen and Doisy fortunately selected the rat for experimentation and obtained results so clean cut and convincing as to remove all remaining doubts

In their first experiments they collected follicular fluid from the ovaries of hogs and used it in its untreated form When injected into the body cavity of newly weaned rats, it had the astonishing effect of bringing them to a state of apparent sexual maturity within three or four days—a process for which normally a period of several weeks is required These results would compare with bringing a girl baby to a condition of puberty in three months Less spectacular, but equally significant, were the effects upon older animals from which the ovaries had been removed The whole genital tract quickly recovered from the atrophy which it had undergone after the operation From their state of apathetic disregard of their

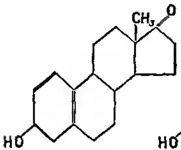
mates, the treated animals began promptly to show a lively interest in masculine attentions. More prosaically stated, they were thrown into the physiological condition of *estrus*, or *heat*. Having no organs for the production of ova they, of course, remained sterile, but otherwise the normal reproductive activities were resumed. The deduction now became obvious that the sexual rhythm is maintained, in part at least, by the periodic discharge of the follicular hormone, a deduction that had, however, previously been reached, though less conclusively, from the fact that such discharge was already known to be periodic and to correspond in frequency with the onset of the estrual state.

In the years that have intervened since Allen and Doisy's first work on the ovarian hormones, these substances have been under intensive, world wide study by chemists and physiologists alike. Of signal use in the identification of the female hormones is the effect which they have upon the structure and secretion of the vagina of rodents. This reaction has afforded the physiological indicator for much of the research of recent years. Two types of active principles have been secured from ovarian tissue. One group of these, known as the *estrogens*, are marked by their ability to bring about estrus in immature, spayed animals. The other principle, *progestin*, is characterized primarily by its ability to bring about changes in the uterus similar to those occurring in pregnancy.

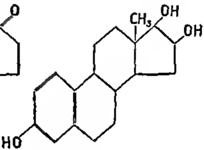
Six years after the first report, Doisy and various colleagues and, independently, Butenandt succeeded in obtaining from the urine of pregnant women an estrogenic principle in pure crystalline form. Chemical manipulation showed it to have the empirical formula $C_{18}H_{22}O_2$. The compound was first known as *theelin*, the name which was assigned to it by Doisy. More commonly it is now termed *estrone*. Shortly afterward, Marrian and then Doisy's group succeeded in isolating from pregnancy urine another substance, designated as *theelol* or *estriol*. It has the formula $C_{18}H_{24}O_3$. Collip and his associates obtained a similar active substance from placental tissue

and called it *emmenin*. It was found to be a water soluble complex of estriol compounds. In 1936, Marrian's group isolated still another substance from pregnancy urine in the form of a sodium salt of *estriol glucuronide*, and identified it as the ester form of the active material in Collip's placental extract.

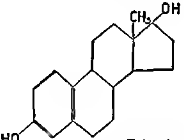
Estrogenic Sterols



Estrone



Estriol



Estradiol

The titer of this substance in the urine serves as an indicator of progestin secretion. From estrone, by a reduction process, it has proved possible to obtain another crystalline estrogen, known as *estradiol*. This material occurs in extracts of hog ovaries and in the urine of pregnant mares. Two other estrogenic sterols from the same source are *equilene* and *equilenin*, but these so far have proved to be of chemical rather than clinical interest.

The pure estrogens are of remarkable potency According to the earlier assays of Doisy, one gram (fifteen grains) of estrone would suffice to bring two million castrated rats into the state of estrus If every woman and girl in the United States were as sensitive as a rat, one ounce of the preparation would suffice to evoke a reaction in the entire feminine populace of this country

Like the active principles of the testes and the adrenal cortex, these various estrogens fall in the phenanthrene cyclopentane group, being made up on a cholane nucleus Following the work of Ruzicka and others, researches of recent years have brought forth a great many active sterols of this type, many of which have estrogenic properties The phenanthrene nucleus, however, is not indispensable for estrogenic activity Robson and Schönberg found, in 1937, that the compound triphenyl ethylene could bring about prolonged estrual change in mice as well as in other animals More recently, much interest has attached to a product described, in 1938, by Dodds and associates, known as diethyl stilbestrol It is about two and a half times as potent as estrone and exerts its influence when taken by mouth It is often effective clinically in dosage as small as one milligram but has the disadvantage of giving rise to nausea, or even vomiting, in some patients Both of the two last mentioned compounds can be manufactured cheaply

The chief *clinical uses* of the estrogens have been summarized by Hamblen as follows In the vaginal epithelium, cell multiplication is promoted, hence, the material is of value in the treatment of gonorrheal vaginitis of children, vaginal hypoplasia or ovarian deficiency, and senile atrophy of the elderly The stimulating effect on the epithelium of the cervix of the uterus is of value in the treatment of ulcerated cervicitis Within the uterus itself stimulation of growth can be induced, hence, the material is useful in the treatment of uterine hypoplasia, amenorrhea, and, paradoxically, excessive bleeding Through its effect on the muscular tissue of the uterus, it is useful to induce abortion and in the treatment of sluggishness

of the uterus during labor In the breasts it induces cellular development in the duct system but suppresses the actual process of milk formation, hence, its principal uses are in the treatment of mammary hypoplasia and undesired lactation In the anterior lobe of the pituitary the estrogens cause reduction in follicle-stimulating gonadotropin and increase in the luteinizing factor By virtue of these characteristics, estrogens may be helpful in hyperfunctional states of the pituitary (menopause, gigantism, pituitary basophilism) and in functional irregularities of menstruation Through their effect on the pituitary, the estrogens lead to alteration of the cyclic behavior of the ovaries and are, therefore, used in the treatment of sterility and underfunction of the gonads Through their effect on the circulatory system also, the estrogens may influence irregularities of uterine bleeding and may be helpful in eclampsia and headache of endocrine origin They may be used also for the halting of skeletal growth to forestall undue tallness in gonad deficiency as well as in preadolescent gigantism Finally, Hamblen regards the estrogens as therapeutically valuable in facilitating the utilization of the corpus-luteum hormone by the uterine epithelium Through this mechanism also they are helpful in correcting menstrual irregularities and dysmenorrhea

It should be emphasized that the estrogens are recent additions to the therapeutic armamentarium and that probably much remains to be learned regarding the best ways to employ them A variety of intricate glandular interrelations are involved and these presumably will all have to be taken into practical account before the use of the sex hormones will have come to full fruition

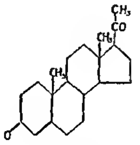
What happens to the estrogens after they are introduced into the body is an important problem about which we have little information In the test tube of the chemist many transformations are possible from one steroid to another To what extent such possibilities are utilized physiologically in the metabolism of the estrogens is not known The facts that all

normal women secrete androgen and all normal men estrogen suggest that the conversion from female to male hormone and vice versa is relatively easy Another chemical problem of much scientific—and potentially practical—significance is the source of the estrogens within the body Theoretically they could be derived from cholesterol, which is widely disseminated in the body tissues and the blood stream and which is the principal ingredient of gallstones Were we informed on this point, possibly something could be done in correcting ovarian secretory anomalies by dietary control

For further discussion of various commercial preparations of the estrogens, their sources and uses, Hamblen's book may be consulted

In addition to the estrogenic derivatives, the ovary produces another active principle called *progestin* In its pure crystalline form this agent is known as *progesterone* The substance is elaborated in the *corpus luteum* of the ovary but cannot be regarded as its sole hormone because that structure produces estrogen also This fact seems to have led to considerable confusion in early researches on corpus luteum material in that estrogenic effects were confused with those of progestin proper While several earlier investigators, beginning with Iscovesco in 1914, had prepared more or less potent lipoid extracts of corpus luteum, it was not until 1928 that reliable chemical findings began to be reported In that year, Hisaw and collaborators succeeded in producing notably active extracts containing the progestational principle and Corner confirmed the earlier work of Ancel and Bouin, proving that the progestational reaction in early pregnancy of animals is due to the action of the corpus luteum Corner and Allen succeeded in producing an extract sufficiently potent to maintain pregnancy in spayed animals Chemical research proceeded actively in several laboratories, leading in 1934 to almost simultaneous success by three different groups of workers in isolating progesterone itself It was found to have the formula $C_{21}H_{30}O_2$. Within the same year, Butenandt verified its structure by

synthesizing it from stigmasterol, a soybean product The same investigator prepared it subsequently from pregnanediol It, too, has a phenanthrene nucleus and is chemically closely related to the estrogenic sterols



Progesterone

The chief *therapeutic use* of this material is in the treatment of threatened abortion and of irregularities in the menstrual function The best results are usually obtained when attempts are made to imitate the cyclic secretion of progestin in alternation with that of the estrogens

CONTROL OF THE OVARIES

Most of what was said regarding the control of the testes applies, *mutatis mutandis*, to the ovaries The principal difference is that the ovary successively secretes estrogens and progestin and these two products have interrelations The evidence now available suggests that there is a double rhythmicity in the production of gonadotropins, the luteal phase in the ovary giving rise to depression of luteinizing hormone secretion to be followed by depression of follicle stimulating hormone when the ovary goes into the phase of follicular dominance These alternate depressions in the pituitary lead to corresponding depressions in the progestin and estrogen formation and thus the alternating cyclicity is maintained

PSYCHOLOGICAL CONSIDERATIONS

What was said in the previous chapter regarding androgenic factors in virility is mostly true, likewise, of estrogenic factors in femininity Early deprivation of the ovaries leads to failure of the temperamental changes normal to puberty Partial ovarian deficiency due to early anterior pituitary depression results in a considerable deficit in sex development, but the psychological concomitants seem to be rather less marked than in males showing comparable degrees of eunuchoidism Rather normal emotional reactivity may be experienced The difference may arise from the fact that a less active role in amatory matters is demanded of women than of men, hence, deficiency of ardor is less disconcerting

In the lower animals, spaying at any age does away completely with all heterosexual interest whereas erotic reactions can easily be brought about by the use of estrogens In the case of women, the arousal of desire by these agents is much less obvious This comes about, in part, from the fact that a considerable amount of eroticism may persist after loss of the ovaries and, in part, perhaps, from a less definitive quality of amatory desire in that sex However, cases are occasionally reported in which women under treatment with estrogens find themselves so much and so consciously stimulated as to refuse to go on with the medication

Hoskins and Wheelon reported in 1914 that ovarian extirpation in dogs resulted in a marked increase in the reactivity of the sympathetic nervous system The well known disturbing effects of the same operation upon women indicates that the central nervous system shares in the augmentation Since, however, low production of estrogens, as seen in girlhood or old age, is a benign condition, it must be assumed that it is the hormone imbalance induced by the operation rather than the deficiency of ovarian hormone as such which gives rise to the menopausal symptoms The captious stridency of the adult hypogonad was previously commented upon.

One of the most revelatory investigations of the relationship of ovarian hormones to personal psychodynamics is that of Benedek and Rubenstein (1939, 1940) One of the investigators studied the daily temperature charts and the character of the vaginal secretions of a group of women who were undergoing psychoanalysis The other somewhat elaborately analyzed the patients' dreams Each physician, on the basis of his own data, made up independent charts of the menstrual cycles When the charts were compared, it was found that both technics were able to indicate the various significant phases of the cycles and that the charts almost exactly coincided Briefly, it appeared that while the women were under the dominance of their follicular hormones they were oriented outwardly and their emotional adjustments and maladjustments centered in heterosexual relationships In short, as in the lower animals, the estrogens were found to be playing their basic role, namely, to bring about sexual activity During the period when follicular dominance merged into corpus luteum control a brief state of ambitendency was found It was marked by the appearance of more or less flighty irritability Finally, as progestin came into control, the psychic orientation changed from the outer world to the woman's own person with special concern for bodily welfare The new evidence served to indicate that, both psychologically and somatically, the corpus luteum is concerned with the establishment and maintenance of pregnancy and has the basic function of conserving the welfare of the newly created being during its sojourn within the body

Thus, it appears that in women, just as in men, the biological relationships having to do with reproduction are fundamentally under hormone control The operation of these factors is much less clearly evident in the human than in the infrahuman forms, however, because the primary biological tendencies are greatly modified by cultural patterning as well as by immediate social relationships

In *summary*, we may say that the ovary has the dual function of forming the female sex cells, the ova, and the pro-

duction of two sorts of hormones, the estrogens proper and progestin It is probable that estrogens are formed throughout life from the fetal stage to the menopause Progestin is formed only during the active reproductive years Early removal of the ovaries leads to persistence of the prepuberal bodily and mental characteristics throughout life, except that body growth equals or even exceeds the normal The secondary sexual characteristics depend, both in their development and in their functions, upon ovarian hormones Estrogen serves as a general sex stimulant and, in animals, brings on the condition of estrus Progestin adds a secondary stimulation that serves to prepare the uterus for the reception of the fertilized ovum and to regulate various of the processes of pregnancy These hormones play a role in the emotional life and personality of women comparable to those of the gonadal hormone in men

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VIII. THE PLACENTA AS AN ENDOCRINE ORGAN

THE PLACENTA is an organ that serves primarily as a transfer station between the mother and the growing fetus It is a complex structure made up of contributions from both The ovum almost immediately after fertilization divides into two cells and these, in turn, into four, eight, etc It reaches the uterus while still consisting of a minute spherical mass of individual cells A highly complex series of developmental changes then ensues The organism soon comes to resemble a chestnut burr within which the body proper early becomes demarcated as a larvalike being surrounded by an envelope By the process of *nidation*, the whole structure becomes partially imbedded within the wall of the uterus The little projecting fingers of the fetal envelope grow in length and branch into subdivisions These penetrate the uterine tissues, which become strikingly thicker and more vascular The uterine capillaries enlarge to form lakes of blood in which the branching fetal rootlets are submerged From these lakes they abstract nourishment and oxygen brought to them through the circulation of the mother Into the lakes are discharged the waste products of the fetus As the pregnancy progresses, both the fetal and the maternal components of the placenta continue to increase in mass and complexity At the end of the gestation period, the organ is a disklike mass some eight or ten inches in diameter that weighs about three pounds As the fetus enlarges, its connection with the placenta becomes more and more remote until finally, at the time of birth, the sole communica

tion is through the umbilical cord, a structure some two feet in length

For a long time biologists were content to see in the placenta merely a device for metabolic exchange between the mother and the growing infant But gradually speculation arose as to whether it might not have other functions As early as 1913, Fellner succeeded in making potent extracts of the placenta Thus, the organ was shown to be at least a storehouse, if not a producer, of sexual hormone At first, the former alternative seemed much the more likely Under the microscope the placenta fails to reveal the common characteristics of a secreting gland It was not until technics were evolved for the detection of the sex hormones in the blood and urine of the pregnant woman that the problem could be put to actual experimental test If the placenta merely stores hormones produced by the ovary, removal of that gonad should result in the early disappearance of its secretion from the circulation Waldstein has shown, however, that estrogen continues to be detectable in the blood and urine of women whose ovaries have had to be removed after the third month of gestation Furthermore, the concentration of this principle increases up to the end of pregnancy whereas no comparable increase of the activity of the ovary can be detected Indeed, the corpus luteum, which in its earlier stages at least produces estrogen, actually shows regression toward the end of pregnancy Altogether, then, the evidence seems clear that the placenta actually secretes estrogen and that this substance increases in amount throughout the duration of pregnancy

By treatment of fresh human placenta with acetone and then extraction of the acetone fraction with alcohol, Collip secured an active substance that he named *emmenin* As previously mentioned, this subsequently proved to be a complex of estriol glucuronides It differs in one important respect from most other sex stimulating hormones in that it is fully active when administered by mouth In suitable dosage it has the further remarkable property of stimulating the sexual maturity

of infant rats without other complicating effects Within three to five days after the beginning of treatment the baby animals come into heat If the treatment is continued, the estrual cycles thus set up continue in fairly normal rhythm Examination of the ovaries gives no evidence that their development has been significantly affected Notably, they do not show any exaggeration of corpus luteum formation such as follows the implantation of anterior pituitary grafts The use of larger doses of emmenin serves to throw the animal into a state of continuous estrus, which persists until the normal age of puberty, after which regular cycles of sex activity followed by quiescence supervene Emmenin has no significant influence on the sexual activities of normal adult animals and is without effect in young animals from which the ovaries have been removed Unlike anterior pituitary products, it has no influence on young males Collip interprets his results as indicating that the placenta produces in emmenin a hormone that has as its sole function the accentuation of the secretion of estrogen He further believes that the regulation is so delicate that the production of that hormone ceases when its normal level has been reached Proof of the assumption first mentioned is found in the fact that grafting the ovaries of infantile rats that have been treated with emmenin into adult castrates causes sexual reactivation in the hosts, whereas ovaries of untreated infants have no such influence

As to the rationale of the production of this hormone we can only speculate Obviously its outstanding characteristic, the activation of the immature ovary to produce estrogen, could play no part in the normal life processes because immature females by no natural possibility could become possessed of a placenta Presumably, therefore, the hormone naturally serves for the relative overstimulation to estrogen production during pregnancy which, in turn, serves to promote certain of the activities of that state

The production of estrone and of emmenin does not comprise the full story of the hormone activities of the placenta

It produces at least a third substance which has properties similar to those of anterior pituitary gonadotropin Collip designated it the *anterior-pituitary like hormone* and it is frequently referred to as "APL" When injected into infantile rats, APL serves within three to five days to bring them into a state of sexual activity If the dosage is kept down to the minimal effective amount, the characteristic appearance of estrus is noted in the vagina but little change is seen in the ovaries At most, they show only a slight increase in weight with slight over development of the follicles When the amount of extract is increased two or three times, the ovaries show a strikingly greater response In brief, they are quickly brought to the stage of development of the young adult Normal, newly formed corpora lutea are in evidence and a crop of actively developing graafian follicles is seen It is especially interesting that the ovarian activity halts at the normal stage rather than going on to excessive corpus luteum formation, with the resulting suppression of estrus that is commonly obtained with pituitary preparations The injection of moderate amounts of this substance into adult females has no perceptible influence upon the sexual activities except occasional slight irregularities in the cycles Collip's animals so treated mated normally and produced and reared normal litters Such animals showed no hypertrophy of the ovaries The substance has no significant effect on animals from which the primary sex glands have been removed Likewise, it does not affect bodily growth

Unlike emmenin, APL has a striking effect in males While the testes themselves increase but little in size, the accessory sex organs, the seminal vesicles and the prostate, show a remarkable hypertrophy It would seem, therefore, as Collip says, that the hormone induces the testes to work rather than to grow It is effective, too, in causing descent of the testes in cryptorchid boys

Altogether, this hormone would seem to be a pure stimulant for the primary sex glands If the arrangement is purposeful, the effects on the fetus and on the mother must be considered

It may be a factor in stimulating early gonadal development and its effect in cryptorchidism suggests that it may be an important factor in bringing about normal descent of the testes at the close of the gestation period Stimulation of the maternal ovaries could, of course, be regarded as adaptive, the gonadal hormones have an important influence on such processes as breast development.

Collip has shown that a combination of emmenin feeding and injections of APL has an effect entirely different from that of either alone If the latter is given in small dosage, the infant rat is brought quickly into her first estrus By larger dosage she may be kept in continuous heat Similarly, emmenin serves at most to produce a long estrus period Neither extract alone will push the ovary into the state of overactivity that is marked by excessive corpus luteum formation, such as is seen after repeated pituitary grafts or injections of urine of pregnant women Correlated with this result, neither substance alone will serve to set up the normal sexual rhythm Quite a different result is obtained when an animal is first brought into continuous heat by the use of emmenin and then subjected to moderate doses of the pituitarylike extract The continuous estrus is broken up into characteristic rhythmic periods The ovaries after three weeks of such treatment were found to be filled with corpora lutea and, accordingly, to have enlarged much beyond the normal size Both emmenin and APL are excreted freely in the urine of pregnant women

Mazer and Goldstein have cited evidence that the placenta produces another hormone that serves to bring about a corpus luteum reaction in the ovaries This may, however, be a special case of Collip's composite effect, as just discussed

Finally, mention may be made of a somewhat extensive series of observations made by Hammett, fifteen years ago The mothers of one hundred and seventy seven newborn infants were given dried human placenta in daily doses of thirty grains The growth of the infants was compared with that of three hundred and fifty seven whose mothers did not receive

placenta In 60 per cent of the cases the babies of the treated mothers grew faster than the controls Whether this finding should be interpreted as indicating the production of a growth hormone, or as due to stimulation of the mammary glands of the mothers to produce a better quality of milk, has not been decided The latter would seem to be the more probable Apparently, Hammett's experiments have been neither confirmed nor refuted The observations would seem to be significantly related to the remarkable fact that animals—even grass-eating cows—almost invariably consume the placenta after the birth of offspring

Altogether, then, it seems evident that the human placenta plays an important role in support of the pituitary and the ovaries in the regulation of the processes of pregnancy The endocrine functions of the human placenta, however, are apparently shared to only a minor extent by that structure in animals other than the higher primates

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IX. THE PINEAL GLAND

THE EXISTENCE of the pineal gland was known to the ancient Greek anatomists A description of the structure is included in the writings of Galen Its function has always presented a mystery, not only to the ancients but in no small degree to the most recent of the moderns Descartes, in the middle of the seventeenth century, used this organ to extricate himself from difficulty with the fundamentalists of his day Theological dogma insisted upon the existence of a soul but scientists then, as now, experienced difficulty in finding for it a material locus Descartes took the impregnable position that the soul has its seat in the pineal gland Perhaps had he been aware that the organ tends to become filled with stony concretions in adult years, he might have added a further persuasive touch to his formulation Magendie, in 1795, made the more practical, though equally untenable, suggestion that the pineal serves as a sort of valve to control the flow of the cerebrospinal fluid

ANATOMY OF THE PINEAL

The pineal, as its names implies, is a cone shaped body (Latin *Conarium pinealis*, pine cone) It is attached to the brain, opposite the pituitary which, it will be recalled, lies on the under side of the brain in the center of the head

Embryologically, the pineal arises at about the end of the first month of existence, as the *pineal process*, a hollow out growth from the roof of the brain This process becomes en larged at the outer end to form a saclike structure that later develops into a solid mass of lobes, the completed pineal body

It remains attached to the brain by the hollow pineal stalk In the human adult, the organ is about a third of an inch long and weighs some two grains (0 18 gram) In children, it is relatively somewhat larger Beginning at about the seventh year it begins to regress, from which time on it tends to become loaded with sandlike concretions of calcium salts—*brain sand* Contrary to earlier belief, it persists in fairly definite anatomical integrity throughout life

Under the microscope the pineal fails to give much evidence that it is a genuine secreting gland It is made up largely of supporting tissue rather than active elements, though it contains a considerable amount of pigment, some fatlike material, and certain cells that in a measure resemble those of typical secreting glandular tissue The fact that it has a rich blood supply might be taken as suggestive of an active function rather than of mere persistence of a vestigial organ that in the course of evolution has outgrown its usefulness

In many of the lower vertebrates the pineal is more highly developed than in man In some forms it grows outward through the skull to form a more or less distinct median eye Commonly, this remains rudimentary but in many ancient, as in some modern lizards, the structure served as a true eye with cornea, lens, and retina The pineal is found in all the mammalian group of animals, but is only rudimentary in sloths and their kindred and in whales

Such knowledge as we have of the functional significance of the gland has been derived from administration of pineal derivatives, experimental destruction of the gland, and from post mortem studies in human subjects

FUNCTIONS OF THE PINEAL

Injections of pineal extracts in the hands of several earlier investigators failed to show that it possesses any unique properties not shared by body tissues in general It is true that such injections, when made directly into the circulation, are fol

lowed by a fall of blood pressure and sometimes by an increased output of urine, but the same is true of many other tissue derivatives Such phenomena cannot in themselves be taken as evidence of hormone content of extracts Other later studies have given contradictory results Engel, as well as Rowntree, has reported hastening of sexual development, but other studies have failed to confirm the findings

Feeding experiments, on the other hand, have been somewhat more productive Years ago, McCord and Allen noted a peculiar effect when pineal substance was added to the water in which tadpoles were kept The pigment cells of the skin (*melanophores*) contracted sharply, giving the creatures a striking silvery, translucent appearance in sharp contrast with that of their dark skinned brothers This observation was confirmed by Chidester and the additional fact was noted that the transformation of the tadpoles into frog adulthood was hastened In principle, these findings support an older observation of McCord that the cell-division rate of slipper animalcules (*paramecia*) was doubled when pineal substance was added to the medium in which the organisms were growing It seems fairly well established, then, that this substance does possess a unique quality and that it may be due to the presence of a hormone

Whether this demonstrable efficacy of pineal substance has any significance as regards higher animals is less clear It has been reported that feeding dried pineal material to guinea pigs, kittens, rabbits, and puppies resulted in some cases in acceleration of growth and that, in males at any rate, the sex gland showed precocious development Other experiments, however, have given entirely negative results—especially those made on rats McCord put the problem to a rough and ready test Certain individuals of a litter of puppies were given pineal treatment and the remainder kept as controls The puppies after a time were offered for sale It happened—as a matter of coincidence or otherwise—that all of the pineal fed animals were chosen before any of the controls In any case, such

acceleration of development as may result from pineal feeding halts when the normal degree has been attained No observer has reported the production of either gigantism or ultimate oversize of the gonads such as is readily produced by pituitary extracts McCord was led to believe that pineal substance obtained from calves is more efficacious than that from adult animals When McCord's experiments were first reported, high hope was entertained that pineal treatment might be of use in hastening the development of retarded children, but Goddard, in following up the lead, obtained only negative results

The effects of destroying the pineal in experimental animals have likewise failed of concordance in the hands of different investigators The procedure presents a difficult surgical problem and the great majority of experimental animals in which it has been attempted have promptly died of hemorrhage Of those that survived some, perhaps most, subjects have shown no detectable effects On the other hand, several observers have reported a certain amount of accelerated development when the operation was performed in chicks In males, the testes weighed more than was normal for the age and the comb showed early enlargement This latter is significant of sexual ripening In females, experimental results have generally been negative More recently, two researches have been reported (Yohoh, Izawa) in which the earlier findings of accelerated development following removal of the pineal have been confirmed Izawa obtained positive results even in rats and in both sexes After two months the gonads were a fourth larger than in the untreated controls

A careful restudy of the problem was reported by Davis and Martin in 1940 Young rats, cats, and dogs were used as subjects Litter mate controls of the same sex were used for comparison in all cases In rats, the pinealectomy had no effect on behavior but there was some indication in the males of stimulated development at puberty In female cats, no effects on development were seen but after they gave birth to offspring

they showed a lack of maternal concern and were deficient in milk production The male cats, on the other hand, reached sexual maturity four or five months before their controls and finally became larger than normal cats They were more than usually aggressive and belligerent One male dog also out stripped his control both in sexual development and body size The thyroids, adrenals, and ovaries of the experimental subjects appeared to be normal but the testes and the hypophyses were enlarged

It will be noted that the evidence as it now stands regarding the relationship of the pineal to development is explicitly contradictory So far as positive results have been secured both administration of its substance and destruction of the gland have had the same accelerating tendency The data are not yet sufficiently convincing to justify speculative consideration of the paradox

CLINICAL CONSIDERATIONS

A third method of investigating the pineal is the observation of effects of abnormalities of the gland occurring in human beings In general, post mortem studies have failed to establish any correlation between bodily states and abnormalities of that organ Presumably, it is subject to the same disturbances as are other glands, such as inflammation, degeneration, or failure of development (hypoplasia), but from such mishaps effects have seldom been recognized

A striking exception to this generalization occurs in the clinical condition known as *macrogenitosomia praecox* This is a rare disease that is sometimes found in association with pineal tumors The name of the disorder largely describes it The polysyllabic appellation transliterated from the Greek into English is "early enlargement of the genitals and of the body"

The literature on this topic was reviewed in 1927 by Haldeman Among many cases of pineal tumor he found accounts of sixteen in which sexual precocity had occurred All these sub

jects were males and the abnormalities had been detected between the ages of three and sixteen In a typical instance, the subject at the age of five was a "Hercules in miniature," burly in figure, with low pitched voice and the beard and sex organs of an adult. In several of the reported cases, a somewhat comparable precocity of mental development has been noted It is stated, but perhaps none too reliably, that patients are prone to enter into discussions of such suprainfantile topics as the immutability of human destiny It is probable that many cases of this disorder have failed to reach the attention of physicians because of submergence of the abnormality in the normal development of puberty

In addition to instances in which tumor of the pineal has been demonstrated, a considerable number have been reported in which the involvement of that structure was only presumptive The situation is complicated by the fact that a very similar precocity of development may result from overactivity of the adrenal cortex, the anterior lobe of the pituitary, and the primary sex glands

Most observers are inclined to regard the pineal tumors associated with precocious development as destructive in type In a unique case of complete absence of the pineal, that reported by Zandren, the subject, a boy of sixteen, had shown no signs of puberty The testes were like those of a two-year old child

In the intensive development of the field of endocrinology, of recent years, the pineal has been largely neglected While it is true that negative results have not infrequently been the sole reward of the investigator, enough positive data have been secured to invite further study The evidence as it now stands is curiously paradoxical If, as is usually supposed, pineal tumors that give rise to precocious development are of the destructive type, the pineal would seem to have a function of holding back the processes of maturity until the time of their normal onset This presumption is supported by the trend of the evidence that experimental destruction of the

gland, when effective at all, leads to precocious development But Zandren's case is of opposite implication As regards both pineal tumors in man and gland destruction in experimental animals, however, the possibility remains open that the effects are due, not to any interference with hormone production, but to associated disturbances set up in the brain Such ambiguity does not attach to the results of feeding experiments Here the only obvious way of going astray would seem to be a confusion of the effects of the administered pineal substance, merely as protein food, with the effects of any hormone contained in the material Since the earlier period in which negative results were largely secured, much knowledge has been gained regarding effective methods of processing gland materials Repetition of the experiments, utilizing the newer technical methods, might yield more satisfactory rewards Multiple grafting of living gland tissue, such as proved enlightening in study of the pituitary problem, might also lead to significant results

Altogether, the evidence regarding the physiology of the pineal gland is notable chiefly for its inconsistency and inconclusiveness Such weight as it does have serves to suggest that the gland produces a hormone which helps to regulate the rate of bodily development and the onset of puberty More research on the problem is needed

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X. THE THYMUS GLAND

THE THYMUS, like the pineal gland, was known to the ancients It was first described by Rufus of Ephesus some two thousand years ago To the moderns it often appears on the dinner table as "sweetbreads," though the pancreas more commonly figures as this viand The first inkling of its importance in the bodily economy was recorded by Plater in 1614 He reported that at the autopsy of a five months' infant who had died of suffocation an enlargement of the thymus gland was found In 1830, the thymus again came to medical attention in the writings of Kopp, who also reported on "thymus death in childhood" A classical discussion of the gland was published by Friedleben in 1858

ANATOMY OF THE THYMUS

The thymus is located above the heart in the region where the chest cavity narrows to disappear in the root of the neck It is a soft, whitish mass made up of two lobes, the left of which is commonly the larger Under the microscope it is seen to consist of two kinds of tissue, the *cortical* on the outside and the *medullary* within Imbedded in the medullary portion are a considerable number of unique structures, the *corpuscles of Hassall* These corpuscles are, in general, roughly spherical in shape They vary in size and number, and in some animals they are entirely lacking Nothing is known as to their precise function, but they have been reported to increase following some types of intoxication Aside from supporting tissue and the Hassall's corpuscles, the thymus consists of a mass of *lymphoid*

cells quite similar to those that mostly make up the tonsils, lymph glands, and the spleen The structure suggests that, as many physiologists believe, the chief function—if not the only function—of the thymus is to produce white blood corpuscles (lymphocytes)

In the human *embryo* the thymus, like the thyroid and the parathyroids, takes origin at the early, fishlike stage of development All three structures are formed of tissues arising as a part of the gill apparatus The thymus appears as a hollow, cylindrical outgrowth from the third, and sometimes the fourth, gill pouch The cavity soon closes up and the whole rapidly growing mass migrates down the neck to its final position in the upper thorax At birth it weighs from a fourth to a half ounce It is pinkish in color due to its rich blood supply

In the human species the thymus begins to decline in relative weight at about the thirteenth year, but the association of this *involution* with puberty is not generally found among animals (Cowdry) A correlation that does seem to hold, however, is that the mass of the thymus decreases as the relative proportion of lymphoid blood corpuscles changes from that of the juvenile to that of the adult years During the involuntary period the pinkish color is lost and the tissue becomes first gray and then yellowish owing to decrease in its blood supply and increase in the relative amounts of connective tissue and fat Contrary to earlier belief, the gland commonly persists in an attenuated form even into old age The size of the gland is variously reported by different observers When at its largest, at about the time of puberty, it weighs, in man, somewhat more than an ounce, but it is characterized by a great deal of variability from one subject to another It is especially susceptible to changes in the state of general body nutrition, in emaciation it is greatly reduced The gland is relatively larger in castrated than in normal animals and, according to Tandler and Gross, this is true in man It is said to decrease in size during pregnancy

In the lower animals the thymus is found as far down in the

scale as the primitive fishes In these it is rather epithelial in character, that is, its tissue resembles that of an ordinary gland as it does, indeed, in the early stage in man In birds, reptiles, and most fishes, however, it is made up mostly of lymphoid tissue as above described According to Cowdry, the thymus may be regarded as the descendant of a gland which originally poured its secretion into the alimentary canal but which has since undergone a complete transformation to the lymphoid type of tissue, as vestigial organs, generally, have a tendency to do

THE FUNCTIONS OF THE THYMUS

More and more, researches of recent years have continued to cast doubt upon the standing of the thymus as a member of the endocrine congregation Since, however, it is frequently classified among the hormone producing glands, a discussion of the evidence may not be amiss

Studies on the functional significance of the thymus have chiefly comprised observations upon the effects of removing it and of injecting extracts of it into experimental animals Such studies have been supplemented by feeding experiments and by investigations of the structural condition of the gland under various experimental and clinical conditions The literature has been ably reviewed by Park and McClure

Apparently the first investigator to concern himself with the effects of thymus extirpation was Restelli, whose work was published in 1845 Nearly all of his ninety-eight experimental animals—sheep, dogs, and calves—soon died In 1858, Friedleben removed the organ from three goats and fifteen dogs, though the extirpation was incomplete in about half the subjects It was concluded that the gland is not essential to life, but that if both it and the spleen are lost the result is fatal because of the resulting disturbance in blood formation He came to the belief that the thymus, although not indispensable, has important relationships not only with blood formation but also with nutrition and growth

Basch made an extensive series of removal experiments (1902–1908) The results of this work have been extensively reported and have to a considerable degree formed the basis of various ideas regarding thymus physiology that have had rather wide currency since that time Basch emphasized the desirability of working on animals at as early an age as possible In seventeen of twenty litters of puppies, he succeeded in keeping alive at least one experimental animal and one twin control Within two to three weeks after the operation, changes began to be noticed The bones seemed to be softer and more flexible and the gait became awkward The changes suggested that a condition of experimental rickets had been induced, but Basch concluded on account of the relatively short duration and generally mild character of the symptoms that the disorder was not true rickets Nevertheless, that idea was introduced into the literature and it still continues occasionally to be revived

The work of Klose and Vogt (1910) has been widely quoted in textbooks Their most striking results were secured when the thymus was removed from puppies during the second week of life From two weeks to two or three months apparently nothing happened except that nutrition seemed somewhat depressed Then followed a "period of adiposity" The dogs ate ravenously and became fat They showed growing feebleness of intellect and became "dreamy and melancholy" After two or three months this feeble mindedness progressed to "thymic idiocy," a condition that was accompanied by marked loss of weight During this period the bones became so fragile that spontaneous fractures were likely to occur and the dogs were easily susceptible to infection The hair became dry and fell out Prostrating weakness then developed and the dogs died in collapse If the gland was not removed until the sixth week, merely passing symptoms or none at all appeared

Subsequent experiments in several other laboratories gave somewhat varying results, but on the whole seemed to support the findings of Basch and of Klose and Vogt Especially, it was

thought that the thymus has considerable physiological significance in protecting the individual from the condition of rickets

The subject of experimental thymus deficiency in dogs was intensively restudied by Park and McClure in 1919 Their results were essentially negative From their own studies and careful analysis of the literature, they came to the conclusion that "there are other explanations than deprivation of thymus function for the symptoms and pathologic changes which have been reported in thymectomized animals, and that those explanations must be seriously considered in the interpretation of all positive experimental findings, and that for the interpretation of the positive experimental findings reported by some investigators those explanations become absolutely essential" Altogether, available evidence from extirpation experiments quite fails to prove that the thymus has any endocrine function A combination of this or any other serious operation with bad hygiene and poor food is undoubtedly conducive to faulty development and bad health That the deprivation of the thymus, as such, plays some part in such a picture cannot even yet be entirely denied but certainly, at any rate, animals without hygienic handicaps can compensate and survive the operation in perfect health

Calzolari, as early as 1898, found that the thymus was larger in a series of *castrated* male rabbits than in normal animals of the same age He concluded that removal of the testes causes a delay in the regression of the thymus that normally takes place after puberty His results were confirmed by Henderson in rabbits, guinea pigs, and cattle Conversely, this same investigator found that in bovines of both sexes that had been allowed to exercise the reproductive function the atrophy of the thymus was accelerated The persistence or enlargement of the gland following castration has been confirmed by other observers In the interpretation of experimental results, the fact seems to have been lost sight of that the thymus is especially affected by changes in general nutrition The appearance of a relationship of the gonads to this gland may be no more

than a special case of reflection of nutritional changes incident to castration or reproductive activity

In 1912–1913, a series of striking observations on *thymus feeding* was made independently by Gudernatsch and by Romeis, observations that promised to throw new light on the physiology of the gland They found that if young tadpoles were given thymus substance they began to grow more rapidly than did untreated controls and that some of them reached enormous size Extending the experiments to rats, Gudernatsch observed considerable increase in the rate of growth and vitality The treated animals were fatter than their controls, had more frequent pregnancies, larger litters, and longer life span Uhlenhuth subsequently repeated the tadpole experiments, using large numbers of the salamander species In his experience, small amounts of the gland substance in the diet had no influence and large amounts actually inhibited development It would seem that the earlier results, then, were due to a fortuitous combination of factors The thymus, being a deficient food, apparently served to prevent the metamorphosis of the tadpoles into the adult forms and, since they remained alive and continued to some extent to grow, the result was large tadpoles—large simply because they could not undergo the final transformation into frogs At any rate, the conclusion was accepted by Gudernatsch that the thymus does not have any function of producing a growth hormone and that his earlier results were due merely to thymus diet as food—perhaps as a good source of amino acids that are necessary to growth

Rowntree and his associates have reported (1934) that an *extract* made by Hanson from the thymus gland of young calves has remarkable effects in rats When injected daily through several generations of parents, striking and increasing precocity of growth and development in the successive litters was seen The fertility in adulthood was also increased The young of the third and succeeding generations grew and matured physically and sexually at an amazing rate The growth

halted, however, short of gigantism Conversely, removing the thymus glands from successive generations of parents was found to result in accruing depression of growth and maturation Unfortunately, other investigators have more recently been unable to confirm these interesting results Ascher, however, has obtained some degree of stimulation from another type of preparation which he calls *thymocreseine* It was reported that this substance is antagonistic to the thyroid hormone in respect to body growth, but synergistic in its effect on development of the gonads It would seem to be not unlikely that such effects as those reported by Rowntree and by Ascher were due to the presence in the extract of growth promoting amino acids rather than hormones

Interesting is the evidence of Riddle in regard to a relationship of the thymus to egg production He discovered that pigeons occasionally lay eggs that are deficient in the shell and in the albumen layer which surrounds the yolk At autopsy such birds were found to have defective thymus glands It was further discovered that feeding dried thymus substance to the pigeons thus affected resulted in restoration of the ability to produce normal eggs

Many writers have commented upon the relationship of the thymus to various of the endocrine organs The evidence as regards the *gonads* was discussed in an earlier paragraph In 1907, Hedinger made a study of a large collection of material obtained at autopsies in cases of *Addison's disease* In a majority of instances the thymus proved to be enlarged This finding is all the more striking because of the fact that adrenal deficiency is especially characterized by loss of weight and the thymus gland is particularly susceptible to lowered nutrition The total mass of the available evidence indicates that, in general, small or functionally deficient adrenals and large thymuses go together An association of thymus hypertrophy with clinical overactivity of the *thyroid* has also often been reported Again, we should expect atrophy of the gland because of the tendency of hyperthyroid subjects to become emaciated The association

was apparently first noted by Cooper a hundred years ago In 1907, Capelle analyzed the literature then available on the relationship He was able to collect sixty instances of people dying of thyroid overfunction in which autopsy records were available Of those succumbing directly to the hyperthyroidism, 82 per cent showed thymus hypertrophy, and of those whose illness was so serious that surgical intervention resulted fatally, 95 per cent showed that condition Twenty years ago, Hoskins noted that feeding thyroid substance to pregnant guinea pigs resulted in the production of offspring in which the thymus glands were notably enlarged The evidence in general, though by no means concordant, indicates on the whole that the thyroid has a stimulating effect upon the thymus The significance of the relationship is not evident

CLINICAL CONSIDERATIONS

Early in the eighteenth century, Bichat called attention to the association of sudden death of children with enlargement of the thymus gland (*thymic death*) The mishap occurs in much the same way in nearly all cases A youngster apparently in the pink of condition trips over a stone and is picked up dead Or he may be subjected to anesthesia for some trifling operation and succumb with the first whiff of the ether In short, without any outward evidence of the fact, he is fatally vulnerable to any slightly disturbing incident The condition, however, is much more rare than was formerly thought and, indeed, is doubted by many clinicians to be a genuine entity The condition is known as *status thymicolymphaticus* Not only the thymus, but also the other lymphoid structures in the body, such as the tonsils, the adenoids, and the lymph glands, are generally enlarged Status thymicolymphaticus was discussed at length by Paltauf in 1889 In addition to the changes in the lymphoid structures, he emphasized the evidences of inefficiency of the circulatory apparatus As a char

acteristic part of the picture he noted that the arteries, large and small, had thinner walls and were smaller than normal In some cases there were even signs of acute dilatation of the heart and more or less degeneration of its muscular tissue

Enlargement of the thymus may give rise to trouble primarily by causing *pressure* In the upper part of the chest cavity of the young child is found the so-called "critical space of Grawitz" Into this narrow nook between the unyielding thoracic walls are crowded the trachea, the esophagus, and important large blood vessels and nerves When, in addition, an enlarged thymus intrudes into the same narrow confines, serious trouble may result The most common symptom of this contretemps is *dyspnea*—difficult breathing—either continuous or remittent The continuous form is more often seen in very young infants The difficulty often increases until the child has a suffocative attack accompanied by intense congestion of the skin (cyanosis) The attacks come on without warning or follow fits of screaming or crying, particularly if the head is thrown back The attacks are repeated with greater or less frequency and death may occur during one of them Another variety is that in which the child appears to be quite normal until several months of age, when he is suddenly seized with a suffocative attack accompanied by intense cyanosis and often with convulsions After a few moments he commonly returns to an apparently normal state It is possibly the occasional occurrence of this picture which gives rise to a common worry of mothers that any infant may commit unwitting suicide by holding his breath Except in the presence of an enlarged thymus—and this is a relatively rare condition—the mother's fears are quite groundless The breath holding has no other deleterious effect than achieving the child's unwholesome aim of commanding solicitous attention

A symptom that may or may not accompany the liability to dyspnea is *stridor* This is a harsh, high pitched sound, like the whistling of wind, that accompanies the breathing It is most

commonly heard with the intake, but sometimes also as the breath is expelled The stridor may begin with birth, some times before the dyspnea is apparent

Status thymicolymphaticus seems to be more common in some parts of the country than in others Thus, one physician in Cincinnati saw two hundred and twenty five new cases in a single year, and the condition is reported to be frequently seen in the northwestern region of the United States On the other hand, in some regions it is so rare that pathologists even doubt its existence

The condition is relatively easy of diagnosis at the hands of a skilled physician who has the supplementary aid of X ray apparatus If the chest is photographed at an oblique angle, the thymus shows on the X ray plate as an accessory shadow above the heart It can be detected, too, by a skillful diagnostician, by virtue of its effect on the chest resonance Fortunately the condition yields readily to X ray or radium treatment

There is a rare disorder known as *myasthenia gravis*, in which the muscular system becomes progressively weaker until finally extreme incapacitation results Several authors have commented upon the high incidence of enlarged thymus gland in this disorder Nothing seems to be known as to the significance of the association

In *summary*, we have to do in the thymus with a gland of which the endocrine—indeed, the biological—status is curiously uncertain It is so widely distributed among the higher animals as to suggest that it is more than a vestigial organ, a useless reminder of an evolutionary past It is a structure that can be dispensed with and its owner be none the worse for the deprivation There is some evidence that in birds the thymus influences egg production The evidence is rather respectable that enlargement of the thymus frequently accompanies hyperthyroidism and adrenal deficiency, as well as deprivation of the gonads An enlarged thymus in a child may be a dangerous possession, leading—rarely—to respiratory difficulty or sudden death from trivial causes Whether its influ

ence is exerted in any measure by hormone production is an open question In general, enlargement of the thymus is accompanied by overdevelopment of the other lymphoid tissues Hypertrophy of lymphoid structures is commonly regarded as protective—especially against infections Perhaps the most tenable theory, then, is that the thymus enlargement that is associated with the untoward conditions discussed is not so much a cause as a concomitant result of underlying abnormalities of metabolism

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XI. ENDOCRINE ASPECTS OF REPRODUCTION

THE ENDOCRINOLOGY of reproduction in the male needs little discussion beyond that included in the chapters on the testes and the pituitary In a general way, masculine reproductive efficiency is dependent upon a passably good state of physical health, hence upon a fairly adequate supply of all the hormones The male gonads, having reached maturity, apparently need *only* a *normal milieu*—including a *supply* of gonadotropin—to maintain their functional integrity They continue to produce sex cells, and presumably hormone, from puberty to old age, apparently with little or no special control beyond that of the anterior pituitary gland If, as is sometimes asserted, the sex functions of men undergo periodic fluctuation corresponding with those of women, the cause remains still to be determined Even the existence of the phenomenon is too uncertain to justify further discussion

In the female, however, the case is far otherwise Her sex functions are complex and are under highly complicated special control It will largely be the purpose of this chapter to amplify and attempt to integrate the pertinent facts previously outlined To this end a certain amount of repetition may be condoned

As previously mentioned, the evidence, though none too compelling, indicates that the ovary functions in a measure as a regulator of development even in the earliest years of the life of the girl In childhood the physical configuration—and especially the shape of the pelvis—foreshadows the characteristic

form of the woman Likewise, there seems to be a certain, though by no means uniform, difference in temperament between boys and girls Even in the preschool years, the term "sissy" connotes what is commonly recognized in the boy as an unsuitable failure of temperamental differentiation The healthy "tomboy," too, has to endure a certain, but waning, amount of reproach—especially from maiden aunts who over specialize in *femininity* To what degree popular thought is influenced by a foreknowledge of the demands that a future maturity will make upon the children is difficult to decide No doubt, a substantial part of the early temperamental differentiation between the sexes is a result of cultural pressure consciously or unconsciously applied But, on the whole, both *innate characteristics* and *social conditioning* seem to play a part in establishing the differences

PUBERTY

With the onset of puberty, the picture loses its vagueness of outline Even the most emancipated feminine good fellow differs sharply from her masculine pal She may smoke his cigarettes, drink his gin, and acquire a share in his aversion to euphemistic indirection, but a maid is a maid "for a' that and a' that" She still trims her sails to catch the breeze of masculine fancy according to the customs of her generation The wiles of Eve come unbidden to her aid Unwittingly, she assumes her role in nature's great drama and the race goes on Her less sophisticated sister falls in with the plot unresistingly Her blushing reticences at once mark her for the chivalrous regard of her future mate and reveal her as swaying to the rising tide of her hormones

So much for psychology Do what she will to minimize the marks that nature puts upon her, every curve of her body, the very inflection of her voice, sets her off from men The angularities of hoydenhood vanish—in accumulations of adipose tissue Arms and legs, despite a faithful devotion to tennis or

swimming, conceal their strength in the contours of approaching womanhood The mother is foreshadowed in the girl The pelvis widens to form a cradle for the babies that are to be Their nourishment is assured by the development of the breasts

The preliminary preparations having been completed, the curtain rings up on the drama of reproduction—indeed, in a measure anticipates the complete setting of the stage As this is being written, the daily press carries the news of a thirteen year old girl who has given birth to triplets All through infancy and childhood the ovaries have been preparing sex cells that come to naught When the cue is given—and the mystery of that process has not been solved—a graafian follicle for the first time breaks to the surface and liberates an ovum Fertilization now becomes possible This event marks the culmination of puberty The threshold of womanhood has been passed

The arrival of maturity is timed in a measure by climatic factors In the tropics the event may occur as early as the eleventh year whereas in countries beyond the temperate zone it may be postponed five years longer The Eskimos, curiously enough, tend to mature early but the suggestion has been offered that, what with heavy furs and protecting igloos, the girls spend much of their youth under conditions that are actually tropical as far as immediately surrounding temperature is concerned

THE PHENOMENA OF MENSTRUATION

Menstruation itself marks a frustration of nature—the acknowledgment of failure of fertilization It is the culmination of a cyclic process—but one that is promptly resumed The cycle may conveniently be divided into four periods the "resting stage," the "interval stage," the "premenstrual stage," and the "destructive stage"

The *resting stage* comprises four or five days immediately following the period of menstruation proper During the men

strual period, the lining tissues of the uterus had in large measure broken down and been discharged The mucous membrane —the inmost layer of uterine wall—at the beginning of the resting stage is very thin Interspersed in it, at this time relatively sparsely, are found the characteristic uterine glands that secrete the lubricating fluid with which the interior of the organ is constantly bathed The glands are narrow and straight Strictly speaking, the resting stage is not actually such because already the restorative processes in the depleted lining tissue have begun

Throughout the menstrual cycle the conditions in the ovary as well as those in the uterus must be carried in mind During the resting stage, the ovary contains the corpus luteum formed in the previous cycle, but it is now on the wane It is decreasing in size and losing its characteristic yellow color, to become the whitish corpus albicans The latter gradually fades away and need concern us no further At the same time that the corpus luteum is relinquishing the stage, another graafian follicle is progressing toward ovulation It is forming follicular fluid with its contained estrogenic hormone The production of estrogen is aided, too, by the surviving follicular cells of the preceding corpus luteum, as though that structure were serving a last use before reluctant oblivion In the meanwhile, in the departing corpus luteum the production of the more characteristic hormone, progestin, has ceased and the oncoming follicle, freed from its inhibiting influence, redoubles its vigor The estrogen that it is forming is, in part, reaching the circulation and being carried to the regenerating uterine tissues and the interval stage is under way

The *interval stage* lasts for about ten days It is a period characterized by preparations in the uterus for the reception of the now rapidly developing, oncoming ovum with anticipated pregnancy to follow The uterine lining, the *endometrium*, thickens The uterine glands lengthen and become more closely packed The blood supply increases in marked degree

Along with the growth of the endometrium, activities in the

ovary continue. During the first half of the interval stage, events reach their culmination in the developing follicle. Rupture of this structure takes place about midway between the menstrual periods. The ripened ovum escapes, accompanied by a minute flood of surrounding follicular fluid. This is ab-

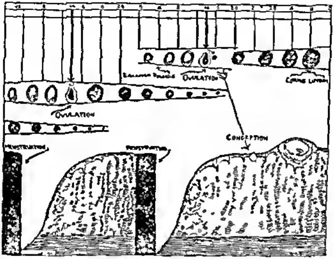

Diagram showing the relationship between the ovary and the uterine changes of menstruation and pregnancy. The lower part of the diagram represents the endometrium with its contained glands. Note the nidation of the early embryo and, further to the right, the attached embryo and beginning placenta formation. Courtesy, Dr. Benjamin Parvey. Published in Endocrinology, 16: 225, 1932.

sorbed and carried to the endometrium, the growth and circulatory supply of which are further stimulated. Rapid multiplication begins in the cells that line the cavity from which the ovum escaped and soon a new corpus luteum is established. In the meanwhile, the production of estrogen continues. The

ovum, now at large in the body cavity, is picked up, if all goes well, by the fingerlike projections of one of the fallopian tubes It is swept along into the tube where it awaits the nuptial con tact with a fertilizing male cell, the spermatozoon The central feature of the drama at this stage is the liberation and absorp tion of estrogen

In addition to the physical changes just noted, as seen in the woman, there also occurs in the female of lower species a striking psychological reaction Her previous complete disdain of the male is succeeded by a lively approbation of his gallant attentions Should these not be spontaneously forthcoming, she is not above offering the most flagrant suggestions The reaction is known as "heat" or *estrus* It is obviously nature's signal that all is organically in readiness for the onset of preg nancy In the evolution of the human species, however, this signal system has largely been covered over, though some women are said to experience a conscious increase of the sex impulse at this time—the mid menstrual period According to Benedek's studies, the intimate psychodynamics now take on a preponderant heterosexual orientation The flood of estrogen having been absorbed and the new corpus luteum having begun to secrete progestin, the interval stage is at an end and the scene again changes

The ten days' *premenstrual stage* now begins The prepara tory processes begun in the endometrium under the influence of estrogen continue for a brief period under the simultaneous stimulating influences of that hormone and of progestin The uterine glands continue to develop in diameter and in length so that they have to assume a corkscrew form to be accommodated within the depths of the endometrium They become distended with secretion The progestin now assumes dom inant control of the situation and the endometrium finally reaches its maximum thickness in full preparation for preg nancy The ripened ovum is now in the fallopian tube If fer tilization occurs, the corpus luteum, instead of degenerating,

as it had before, persists and even increases its production of progestin Consciously or unconsciously, the emotional concern shifts to the body and its welfare (Benedek)

Failing fertilization, however, the secretion of progestin soon ceases and the final *destructive stage* of the menstrual cycle sets in From the congested capillaries of the endometrium, blood cells escape into the tissue The outer layers begin to break down and with their disintegration the minute blood vessels rupture and the menstrual flow is fully established During the four days that normally comprise this period, the dismantling process in the endometrium is completed, the detritus is all discharged, the ruptured blood vessels are closed, and a new cycle begins

In addition to the chain of events just portrayed, researches on monkeys, and especially those of Hartman, have shown the existence of another, the *anovulatory*, type of menstruation That is to say, the uterine discharge sometimes takes place without preceding ovulation The findings suggest that, on occasion, the menstrual function can be promoted by the pituitary with little help from other endocrine agencies A considerable number of instances are now on record in which menstruation without ovulation has been proved at operation in women also, but the phenomenon is rather exceptional

The story as thus related, although somewhat complex in details, can be organized as a straightforward narrative Before this was possible, however, many years of patient research were required A few of the problems initially presented will bear further discussion

Our scientific predecessors early recognized the similarity of the sex cycle in the lower animals and in our own species The most prominent feature in the lower forms is the onset of heat This is often accompanied by discharge of fluid and the suggestion is strong that estrus corresponds to menstruation Numerous attempts to unravel the mystery in accordance with this misapprehension led only to bewildering paradoxes It was not until the period of estrus was shown to coincide in

animals with the discharge of the ovum, whereas that event takes place midway between successive menstrual periods in women and other primates, that the sequence of events could be correlated

When the menstrual period was regarded as the human homologue of estrus, a paradox was presented by one aspect of Jewish ritual Estrus is the time when animals are at the height of their fertility If this were true also of women, then the Jewish custom of interdicting marital relations within the seven days following menstruation should have resulted in a low degree of fertility of these people The Jews are not infertile It would now appear that the interdiction is a device wholly consonant with the injunction, "Increase and multiply and replenish the earth" The compulsory abstinence no doubt plays a part to insure that the ovum upon its arrival in the fallopian tube will be met by fertilizing cells

In recent years, the problem of the relationship between ovulation and menstruation has been studied in the higher primates by methods of direct observation With the aid of surgery the ovaries of monkeys, whose sexual cycles largely resemble those of women, have been examined at intervals after the beginning of the menstrual flow Freshly ruptured graafian follicles have been found in the mid period of the cycle and newly discharged ova have been recovered from the fallopian tubes Similar observations have now been made upon human subjects also Allen and Pratt have carried the study to the point of actually recovering the ova In their experience, these are never found in the tubes earlier than the twelfth day nor later than the sixteenth day from the beginning of the preceding menstruation The appearance of the ova themselves showed that they had been but lately discharged and the signs of recent rupture of the ovarian follicles completed the evidence Doubt can no longer be entertained that in women the discharge of sex cells—ovulation—takes place midway between the onset of two successive menstrual periods

The period of maximal fertility must therefore occur at

this time While in the human species there is perhaps no invariable *period of infertility*, this condition is approximately reached in the last week preceding menstruation This follows from the fact that the ovum within a very few days after its discharge becomes incapable of fertilization and is discharged The sperm cells also retain their vitality for only a relatively short time after their introduction, after which they, too, perish It follows, therefore, that when intercourse is practiced during the last week of the cycle, there is no ovum present to be fertilized and the sperm will themselves have lost their vitality before the next succeeding ovum is discharged

While the foregoing statement covers the situation under ordinary circumstances, the assumed regularity of activity not infrequently fails, hence, marital relations, even when restricted to the so called infertile period, may be fruitful Indeed, it is believed by some physicians that marital intercourse may lead in women—as it normally does in rabbits—to discharge of the ovum, thus in itself establishing premature fertility

The fact that the menstrual cycle is immediately determined by events in the ovary in a measure accounts for its periodicity But the problem remains what regulates the ovarian regulator? This question has been studied most satisfactorily in the rabbit As mentioned above, that animal is peculiar in that the crucial event in the sex cycle, the discharge of the ovum, takes place normally only after the act of mating It can be induced, however, by subjecting the female to implantation of anterior lobe pituitary tissue Similar results can be obtained by the use of sufficient doses of anterior lobe extract About eleven hours are required after the treatment before the process of ovulation takes place Experiments indicate that this is approximately the interval that normally occurs in rabbits between coitus and ovulation Mating in a female deprived of her anterior lobe does not result in ovulation, but if the operation of removing the pituitary is deferred for an hour after the coitus ovulation does takes place The conclusion follows,

therefore, that the act of coitus results in an immediate reflex outpouring of pituitary gonadotropin so copious as to activate the ovary to discharge the graafian follicle and thus initiate the processes that ultimately culminate in pregnancy

She is a fortunate woman whose life flows smoothly during her menstrual period If she achieves complacency of demeanor it is evidence, often, of self-control rather than of absence of difficulty There has been much discussion of the cause of menstrual tension, but a simple and apparently tenable explanation can now be offered Physicians are rather prone to ascribe it to excessive hormone stimulation, but it will be recalled that the menstrual discharge is initiated by a sudden low tide of ovarian hormones Actually, therefore, the woman at this period suffers from a moderate degree of ovarian deficiency In a previous chapter evidence was cited that such deficiency results in increased irritability, especially of the sympathetic nervous system If prolonged, it may result even in change of disposition A similar overthrow of nervous balance is likely to be experienced at the menopause, a condition likewise marked by diminishing ovarian hormones Fortunately the period of ovarian deficiency during the menstrual cycle is of brief duration and by the time the flow is over usually the nervous irritability has disappeared Actually, how much of the menstrual tension is physiologic and how much neurotic is open to question Women who escape the unphysiologic mores of "civilization" are likely to be little disturbed by it, if they experience it at all.

The ovarian hormone tide rises to its height during the premenstrual period Many women recognize this as the time of their greatest efficiency, the time when the feeling of well being is at its maximum Likewise, the basal metabolic rate—an index of the bodily functional level—is at its highest point during the premenstrual stage and reaches its low ebb at the time of flow Lee has noted a comparable cycle in the basal rate of rats As a practical technical matter this depression of basal metabolism is often obscured by irritability of the sub-

ject, a condition that renders difficult the attainment of suf ficient relaxation to give a true basal level for the test Pre sumably, this secondary disturbing factor accounts for the fact that certain investigators have failed to detect the fall in the basal rate.

PREGNANCY

The preparatory changes looking toward the onset of preg nancy have been recounted in relation to the phenomena of menstruation This latter event, as previously emphasized, marks a frustration of nature's purpose Menstruation is con tingent upon sudden cessation of ovarian hormone production This, in turn, is brought about in some way by failure of fer tilization of the ovum The precise mechanism involved here is not understood

We can only say that if fertilization does takes place a new train of events ensues The corpus luteum, instead of proceed ing to rather prompt regression, continues as an actively secret ing structure The endometrium that had been prepared for the process of *nidation* continues its development toward *placenta* formation During the first phase of pregnancy, events are largely controlled by the corpus luteum hormone In the lower animals the influence persists well into the pregnancy But in women, after the third week of gestation, removal of the corpus luteum fails to bring the pregnancy to an end, hence its essential relationship to this condition must have terminated within that period, after which placental hormones are available for control In the lower animals, on the other hand, deprivation of the corpus luteum at any time until preg nancy is well advanced results in abortion According to Frank, progestin is critically necessary in the human species only during the first 5 per cent of the gestation period In the guinea pig 11 per cent, in the rabbit 30 per cent, and in the dog 45 per cent of the total pregnancy period is dominated by that hormone

If the ovum becomes fixed in the uterus its outer envelope,

the *chorion*, undergoes rapid development and, according to the best of the evidence, early begins to elaborate a regulatory hormone Under its influence in association with that of estrogen, together with a hormone from the anterior pituitary and perhaps other placental hormones, the various bodily changes incident to pregnancy take place These changes are fundamental and far reaching, to permit the mother to meet the metabolic needs of what is actually an insistent parasite, the developing infant The growing organism is constantly abstracting from the blood stream of the mother the numerous chemical elements necessary to its growth and differentiation At the same time, it is adding to the stream a variety of waste products for disposal The maternal structures that have to do with the carrying and ultimate expulsion of the offspring undergo hypertrophy The inner layer of the uterus thickens somewhat, generally, but it is that part in immediate contact with the enlarging chorion which undergoes special development to give rise to the placenta. The muscular wall of the uterus increases markedly in bulk, due principally to enlargement of the individual muscle cells This increased bulk is taken up by the constantly greater spread of the uterine wall to surround the growing contents, hence, at the time of birth of the infant, it is stretched to even less than its initial thickness At the same time, the walls of the vagina expand, become more vascular and more freely lubricated—all changes to facilitate the passage of the infant to the exterior Of similar utility is the relaxation of the ligaments of the pelvis that takes place The numerous other details of the bodily changes in the pregnant state need not further concern us in a book devoted to the internal secretions

We are especially concerned with what happens in the various endocrine glands For the most part, endocrinology has not yet progressed to a sufficient degree to permit direct detection of the hormones in the blood stream But so copious is the supply of two of these during pregnancy that they can be thus recognized

The *estrogen content of the blood*, like that of the ovary, gradually rises from the end of menstruation to the latter part of the premenstrual phase of the cycle If pregnancy does not occur, it rapidly falls to a low level during the menstrual period On the other hand, if pregnancy does result, the estrogen of the blood decreases to a considerably less extent According to Mazer and Goldstein, the decrease continues slowly to the end of the second month, after which it progressively rises to a level at the end of gestation considerably higher than that of the premenstrual phase of the cycle Much of the estrogen produced during pregnancy, however, is not taken up from the blood stream but is discharged in the urine According to Zondek, the amount of such excretion rises from something less than one thousand "mouse units" per liter of urine during the first month to approximately ten thousand units in the last month (a mouse unit is the least quantity that will evoke a definite response in the test animal) This high output is correlated with the relatively enormous development of the human placenta In the lower animals it is a much less elaborate organ than in women, and little or no excretion of estrogen by the kidneys takes place in them

In addition to estrogen, the blood contains also a demonstrable amount of *anterior-pituitary sex hormone* This can be shown by a marked hypertrophy in the genital tract of immature mice into which blood serum of pregnant women is injected The hormone content in the urine progressively rises to about six thousand mouse units per liter in the fifth month and gradually falls off to about half that amount in the last month of pregnancy The excretion of both the estrogenic and the pituitary hormones falls to negligible amounts after the birth of the infant

This discharge of estrogen and anterior pituitary hormone is the basis of biological tests for the existence of pregnancy For a variety of reasons, the early recognition of this condition often is important, whereas the classic early diagnostic signs of pregnancy are commonly so ill defined as to render

conclusive diagnosis impossible during the first third of the gestation period Now, by the injection of small amounts of the urine of the woman into test animals—mice, rats, or rabbits—and by noting the effects on the internal genital structures, a diagnosis can be made with a high degree of accuracy

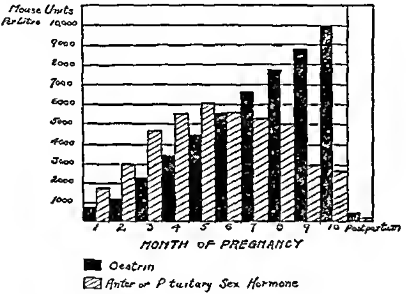

Diagram showing the daily rate of excretion of estrone (oestrin) and of anterior pituitary sex hormone From Clinical Endocrinology of the Female *Courtesy, Drs Chas Mazer and Leopold Goldstein and the W B Saunders Co*

even within the first month ("Aschheim Zondek test") The sex skin of baboons can also be used as an indicator

In addition to objective proof of the overproduction of anterior pituitary hormone and estrogen, we have strong presumptive evidence of augmented activity in various endocrine organs Under the microscope the anterior lobe of the *pituitary*, as has long been known, shows signs of altered functioning in the increased production of certain elements, the pregnancy

cells In addition to the sex hormone, there is collateral evidence of the augmented production of growth hormone This is manifested by a tendency of the pregnant woman to a coarsening of the features suggestive of mild acromegaly Presumably, the increase of this hormone is for the benefit of the developing fetus

The *thyroid*, too, shows evidence of increased function at this time In about half of the cases palpable enlargement of the gland takes place, while under the microscope it usually appears more active than in the nonpregnant state In a small number of cases the overactivity may progress to a stage sufficient to give rise to signs of actual clinical hyperthyroidism Possibly to be correlated with the overactivity of the thyroid is the fact that the basal metabolic rate commonly reaches considerably higher values than in the nonpregnant state The situation is complicated, however, in that the test actually measures the oxygen consumption of both mother and fetus and the increased rate in considerable degree, therefore, undoubtedly mirrors the state of high protoplasmic activity in the latter

A failure of the thyroid gland to rise to the needs of the situation may be of serious moment to the developing infant Women suffering from thyroid deficiency during pregnancy are likely to give birth to defective infants The resulting condition, congenital or infantile myxedema, was described in an earlier chapter Farm animals in the so called goiter belts, where thyroid deficiency is common, likewise show a high proportion of defective offspring According to Engelbach, pregnant women even outside the goiter belts commonly show a condition of relative hypothyroidism, and in all cases in which the basal metabolic rate is not significantly elevated in the latter months of gestation, both mother and infant will profit by the administration of iodine or of thyroid substance Among other reasons, Engelbach believed such treatment advisable to forestall overweight of the fetus with consequent difficulties

in delivery. He maintained that plumpness in a newly born infant commonly represents, not blooming health, but mild myxedema.

The evidence, although somewhat contradictory, suggests that enlargement of the *adrenal glands* also occurs during gestation. Such hypertrophy might be interpreted as an adaptation whereby the accompanying processes are facilitated. At any rate, it is stated that experimental animals deprived of their adrenals when in the pregnant state promptly abort, whereas the administration of cortin serves to prevent that outcome. Hartman has found that greater amounts of cortin must be administered to pregnant animals than to normal controls to keep them in health following the removal of the adrenals. It has also been reported that the administration of adrenal cortex is effective in the treatment of "pernicious vomiting of pregnancy."

The increased liability of pregnant women to tetany has been a matter of common medical knowledge for many years. Erdheim noted that pregnant animals are unusually sensitive to *parathyroid* deficiency. Total destruction of these glands commonly causes the prospective mothers to abort, if not to die in violent convulsions. Richardson has published the results of a study which suggests that a large proportion of pregnant women suffer from some degree of tetany (hence parathyroid deficiency)—especially in the second half of the gestation period. Severe spasm of the calf muscles is cited as a frequent manifestation of the deficiency, though perhaps postural difficulties incident to childbearing play a part here. It is commonly believed that the demands of the growing fetus for calcium and phosphorus needed for skeletal development cause a depletion of these elements in the mother. Such depletion would serve to aggravate the manifestations of any parathyroid deficiency that might exist. On theoretical grounds, any manifestation of a tendency to tetany during pregnancy should be met by the prompt institution of measures to correct the cal-

cium depletion The mere giving of calcium phosphate may be helpful, but in addition vitamin D is frequently advisable to facilitate the utilization of the calcium thus supplied

One of the mishaps of pregnancy against which the alert physician is always on his guard is the condition known as *eclampsia* This is a state of profound intoxication that is likely to take a course of increasing severity manifested by vomiting, convulsions, coma, and death Despite the devotion of many investigators, the fundamental cause of eclampsia is not yet clearly known The intoxication is shown especially by acute degenerative processes in the liver and kidneys, but to what extent these are cause and to what extent effect remains a problem The suggestion has often been made that parathyroid deficiency plays a significant role in the disease and several investigators have reported the glands as defective in that condition, but more research on the problem is needed

Another suggestion that these glands undergo a special strain in pregnancy is seen in the fact that *osteomalacia* is especially likely to occur in that state This is a condition marked by striking loss of calcium in the bones, a condition that has been repocted by various investigators to be accompanied by pathological changes in the parathyroids

If the pineal gland has the relationship to reproduction postulated by various writers, it might be anticipated that this structure, too, might play a role in pregnancy, but animals can go normally through gestation after pinealectomy (Davis)

Whether the *pancreas* is directly concerned is not precisely known In view of the facts that carbohydrate metabolism is largely under the control of the pancreatic hormone and that the growing fetus doubtless makes increased demands upon the mother for a supply of carbohydrate as well as other materials, no doubt insulin plays a role if only in the maintenance of the general health of the mother Certain it is that pancreatic diabetes tends to interfere with all sex activities In the female this disease when of severe grade often causes amenorrhea, sterility, premature menopause, and progressive atrophy of

the sex organs Experimental investigation has shown that complete deprivation of the pancreas in early pregnancy is followed within a short period by the death of the fetus Physicians who have given special attention to the topic assert that about half the offspring of untreated diabetic mothers are either stillborn or so weak that they die shortly after birth The actual incidence of these mishaps is in considerable measure controllable, however, by the proper management of the diabetes There is some evidence that the pancreas of the developing fetus may, in a measure, function in the latter part of pregnancy to correct the insulin deficiency in the diabetic mother In experimental animals suffering from pancreatic inadequacy, events may progress fairly satisfactorily until the birth of the offspring, after which death of the mother from acute insulin deficiency may promptly take place (Carlson) In conformity with the foregoing, Mazer and Goldstein have noted indisputable evidence of overproduction of insulin in an infant of a diabetic mother for several days after its birth The foregoing facts seem to suggest that pregnancy is normally accompanied by overproduction of insulin comparable, for instance, with overproduction of pituitary hormone, but the problem needs further study

Pregnancy, then, is a condition exquisitely dependent upon endocrine factors The preparation for that event is dependent upon estrogen and progestin secreted by the ovary under the influence of pituitary hormones The inception of pregnancy is dependent upon sufficient integrity of the endocrine organs to promote a compatible degree of health in the mother as well as fertility in the father After the pregnancy is initiated, changes take place in the structure of the pituitary and the thyroid which indicate that these organs are undergoing compensatory activity Evidences of increased demands upon the adrenals, the parathyroids, and the pancreas are also available The placenta contributes its hormonal quota Each new human life, then, is borne in upon a hormone tide.

LACTATION

One of the important features of pregnancy is the development of the *mammary glands* to the end that a food supply will be available for the infant upon his arrival into the world This final outcome is the culminating phase of a long train of events

The mammary glands, or breasts, represent ordinary skin glands which have undergone a highly specialized overdevelopment The first indication of the glands in the fetus is a thickening of the skin to form a ridge, the *mammary line*, on either side extending along the ventral body wall In many of the lower forms of mammals this line breaks up into several nodes of development, but in the human species ordinarily only a single region toward the head end of each line continues its progress to any significant extent Occasionally, however, the ancestral bent is betrayed in the development of one or more supernumerary breasts below the primary gland The painter Rubens not infrequently pictured women having well developed supernumerary breasts as a way of accentuating the voluptuousness of his pictures

The physiology of lactation involves two processes that apparently depend upon quite different controlling factors It is expedient to consider, first, the development of the glands, and, second, the stimulation of the developed structures to functional activity

In general, the method of growth is quite similar to that of a tree The early cell mass of the mammary line undergoes a process of multiplication to form a sort of inward growing sprout This branches first into two and this pair in turn into others until the ramification gives rise to a fairly complex *duct system* In some species all the ducts converge to a single unit corresponding to the trunk of a tree In others, the branches come together only at the tip of the nipple just as a shrub may consist of several stems arising from the ground side by side

In the human species there are about a dozen such primary ducts As growth proceeds, the ducts enlarge somewhat toward their outer ends to form the *milk cisterns*

The first phase of development, that is, the production of the duct system, makes little or no provision for actual secreting glandular cells These arise later as little lobes of epithelium (gland tissue) at the terminations of the ultimate branches of the system

At the time of birth of the human infant, only a small amount of true gland tissue is present It is from this that the so-called "witch's milk" is derived This term refers to the fact that from the miniature breasts of the newborn a slight amount of fluid can be expressed The observation is interesting as throwing some light on the control of mammary secretion Apparently the witch's milk is formed as a result of the same hormonal stimulation as that which causes activity in the glands of the mother With the severing of the umbilical cord, the infant's supply of the stimulating hormone is cut off and the secretion promptly ceases

At birth the breasts of the infants of both sexes are closely similar in structure and stage of development. Through the early years of childhood they remain in this latent form One of the first signs of oncoming puberty in the female is renewed activity in the breasts The glandular tissue cells increase in number and size Most of the growth of the organ as a whole, however, is due to gradually increasing deposits of fat in and around the glandular and duct tissue

Unless pregnancy supervenes, the mammary glands persist throughout the active reproductive period of life in an arrested state at the stage of development just described Their size and configuration vary somewhat with the state of nutrition of the woman, but otherwise the internal conditions largely remain constant Some women, however, do experience a slight phase of congestion within the breasts at the menstrual periods This is probably a reaction to the estrogen tide that precedes

the period of flow With the cessation of reproductive functions at the time of the menopause, the breasts commonly undergo a certain amount of atrophy

When pregnancy ensues, further mammary glandular development takes place This is exclusively under hormone control, as is shown by the fact that destruction of the nervous connections of the gland has little or no influence upon events at this time The classic experiment of Ribbert is often cited in this connection He transplanted breasts of guinea pigs to the region behind the ears and allowed the animals to become pregnant Enlargement of the transplanted organs followed, with actual milk secretion when the offspring were delivered

The problem of the hormone control of the breasts has been under active investigation in numerous laboratories for many years Most of the experimental work has been done on lower forms—especially rats, guinea pigs, rabbits, and cattle It has been found that the results differ in details from one species to another, and, indeed, reports are at variance in some respects among different investigators using the same species

First of all, it is to be noted that under normal conditions significant breast development does not occur until the time of puberty and it is prevented by removal of the ovaries In cattle, as Turner's studies showed, each estrual cycle is accompanied by a wave of breast growth and Goldzieher has found evidence of similar cycles in women The ovarian hormones, then, undoubtedly play a role When administered to normal, immature animals—of either sex—estrogens alone cause growth of the duct system and the addition of progestin carries the development into the glandular tissue proper, the *alveolar cells* Progestin alone, however, without estrogen "priming," is ineffective To what extent the ovarian hormones affect the breasts directly and to what extent through the pituitary gland the evidence is not concordant Removal of the anterior lobe causes prompt regression of the developed breasts and the organs can be restored by pituitary grafts or extracts According to some observers, the injection of ovarian hormones is inef

fective in pituitaryless animals but others have obtained fairly well marked reaction In view of the fact that he found the pituitaries of pregnant animals more potent than those of the nonpregnant, Turner postulates the co-operation of a special hypophyseal hormone, ***mammogen,*** in the developmental process

The further evolution of the breasts in the early stages of pregnancy seems to be brought about simply by enhanced effects of the factors operative in the puberal period After the placenta is formed, hormones from it add their stimulating influence The duct system begins to branch and the alveoli to grow to form clusters of *lobules* By the middle of the pregnancy, each lobule resembles a bunch of grapes, the stems being the ducts and the individual grapes the alveoli (Turner) During the second half of the pregnancy, the epithelial cells which border the alveoli gradually enlarge and begin to secrete fluid—the *colostrum* Thus, the alveoli become swollen to many times their earlier size and it is this enlargement, principally, that causes the fullness of the breasts at the end of the period

But the breasts do not begin actual milk formation—lactation—until delivery (or abortion) takes place What it is that holds the process in abeyance is a matter of dispute It is undoubtedly the anterior lobe pituitary hormone *prolactin* which plays the principal role in initiating (and continuing) lactation, but something during the persistence of the pregnancy holds its activity in check This something is probably the estrogenic hormones with which the body is suffused With this influence eliminated, the free flow of the milk can get under way Supporting this assumption is the fact that lactation can be checked after parturition by injecting estrogen

The further progress of the lactation is largely under prolactin control In most instances enough is secreted to keep the flow at an adequate level, but in some women such is not the case Various nutritional influences may play a part and inadequate supplies of both thyroid and adrenal cortex hormones

may be factors Principally, however, the inadequacy seems to be due to underproduction of the mammotropic hormone In a large proportion of the cases the process can be normalized by injections of prolactin, as shown for instance in Kenny and King's (1939) clinical tests In this study, forty three women were given the hormone, two injections a day for five days In 74 per cent of the cases five days' treatment enabled the women to produce enough milk for their babies for the re mainder of the nursing period

So much for the control of the mammary glands There is some evidence—though by no means consistent in details or entirely convincing in tenor—that the glands, in turn, exert a hormonal control on other processes Many women fail to menstruate while nursing their babies This phenomenon has been explained as due to the action of a mammary hormone exerted either directly on the ovaries or through the medium of the anterior lobe of the pituitary to cause a persistence of the corpus luteum which, in turn, holds the cyclic processes in arrest It seems more probable, however, that the hormone having this influence is prolactin itself If the breast does form a regulating hormone it would seem to be relatively inefficient, since a large number of lactating women actually do menstruate and not infrequently become pregnant with or without the previous resumption of menstruation Some women resume this latter function even as early as one month after birth of the child, and about half before the infant is weaned That some interfering factor is operative is suggested by the fact that during lactation menstruation, if present, is frequently irregular and sometimes excessive in amount

THE MENOPAUSE

The active reproductive period in women lasts some thirty five years At about the age of forty seven, on the average, in temperate climates it comes to an end in the so-called *change of life* or *climacteric* In the individual instances, the event may occur a few years earlier or a few years later

The manifestations of the menopause vary a great deal A few women are barely aware of the transition, and the average healthy person experiences only moderate discomfort In a certain proportion of women, however, the menopause is marked by such distressing symptoms as irritability, difficulty in concentration, headache, mental depression, restlessness, and insomnia In a small proportion of cases the nervous symptoms become so severe as to grade into the psychosis *involutional melancholia* These manifestations are likely to be more pronounced in high strung or neurasthenic individuals The sympathetic nervous system shares in the heightened irritability of the transition period Thus is explained a tendency of the blood pressure and the pulse rate to increase under relatively slight stimulation and of the skin to flush easily This latter phenomenon is accompanied by subjective sensations of discomfort, the well known *hot flashes* They can readily be induced in any woman in the climacteric epoch by the injection of a small dose of adrenine (Hannan)

The onset of the menopause is objectively evident by changes in the menstrual function In some cases this comes to an abrupt end with little or no premonition Usually the periods become irregular and scanty and the intervals between periods gradually longer until they cease completely At times, the menopause is ushered in by a tendency to profuse flow, though some physicians regard the latter not as strictly a manifestation of that condition but as a sign of accompanying disease

A condition closely similar to the naturally occurring climacteric is that which results when the ovaries have to be removed surgically at any time during the reproductive years. Like results may be induced by the application of radium The symptoms of menopause when produced artificially are likely to be somewhat more acute than when the condition develops more gradually

It is to be noted that the girl does not suffer from anything comparable with the menopausal symptoms in the early years when the reproductive hormones are at low ebb Likewise,

the difficulties of the menopause at whatever age occurring are but temporary. We must therefore assume, as stated before, that they are due rather to a lack of balance of hormones than to simple deprivation. Is this lack of balance due merely to ovarian failure or must we take into account secondary effects in other glands? The menopause can be induced by removal of the ovaries at any time after puberty. This fact indicates, of course, that it is the failure of hormone production in these glands to which we must chiefly look for an explanation of the phenomenon Moreover, the symptoms can be brought on within a very short period—sometimes only a day or two—after the operation We can hardly assume that other endocrine organs would be sufficiently influenced within that short space of time to contribute significantly to the symptomatology. Likewise, prompt relief of the symptoms from the administration of potent extracts of ovarian substance has frequently been reported—a fact that also suggests the primacy of the gonads Overproduction of pituitary *gonadotropin*, however, is a characteristic feature of the climacteric and this may be one factor in prolonging, if not initiating, the disturbances.

These facts lead us to a consideration of the conditions within the various endocrine glands at the climacteric epoch Under the microscope the *ovaries* show a marked increase in the amount of connective tissue and corresponding decrease in the amount of glandular tissue. Such follicles as have not succeeded in coming to fruition undergo a fatty degeneration and are finally changed into fibrous tissue. The covering layer of the ovaries shares in the fibrous changes, becoming thicker and tougher The suggestion has been offered that this latter change may really be at the bottom of the difficulties—that the follicles are simply so confined that they cannot undergo their normal evolution, i e, come to full development and discharge their contents The estrogen and progestin supply of the body is thus slowly and irregularly brought to a conclusion. It is reported that the ovaries of women who have not borne children show a greater amount of fibrous tissue than do those women who

have Thus may be explained the earlier onset of the menopause in the former group Repeated pregnancies, on the other hand, are stated to result in longer persistence of the active tissue of the ovary, hence a later onset The fact that a certain amount of follicular tissue persists for some time after the climacteric begins is cited by Mazer and Goldstein as explanation of the fact that the atrophic changes that ultimately take place in the lower genital tract are not at first evident According to this conception, as long as follicles continue to develop, even to a limited degree, enough estrogen is produced to prevent atrophy of the uterus and vagina

Much has been written about the relationship of the *thyroid* gland to the menopause The sum total of existing evidence is far from convincing It is notably lacking in consistency Some authors emphasize a tendency to overactivity of the gland and others to the precisely opposite condition The rather lame compromise explanation offered by some is that there occurs an exaggeration of whatever state the thyroid may happen to be in when the menopause arrives The experimental evidence rather supports the belief that functional deficiency is characteristic Commonly, following destruction of the ovaries the thyroid presents microscopic evidence of regression, either in diminution of secreting elements with increase of connective tissue or in the accumulation of colloid In the human species, however, the thyroid at the time of the menopause does not ordinarily become sufficiently depressed to lead to a significant fall in the basal metabolic rate The case is different when actual senility arrives Then the basal rate gradually does diminish This fact may or may not be correlated with the thyroid regression that seems to characterize that epoch many structures other than the thyroid also suffer at that time

A considerable number of women undergo a certain amount of masculinization at the climacteric period of life This is manifested by increased hair growth on the face—especially the upper lip—a change in the pitch and timbre of the voice, and an increased angularity of bodily configuration Some

authors remark, too, upon a masculinization of the disposition, meaning, perhaps, an accentuation of arrogance and self sufficiency. These tendencies to virilism suggest overactivity of the *adrenal cortex*. Supporting the idea is Goldzieher's finding of nodular hyperplasia of these glands.

In view of the intimate relationship of the anterior lobe of the *pituitary* with the reproductive functions, it might be anticipated that changes in this gland would be found to be characteristic. The microscope fails, however, to disclose any very marked alterations As mentioned earlier, increased production of gonadotropin has been demonstrated in the urine of women at the climacteric and both Fluhmann and Mazer have found increases in the blood also But it would seem that the overactivity is comparatively short-lasting. After a few years the phenomenon can no longer be demonstrated. Mazer and Goldstein lean toward the belief that both the increasing obesity that often occurs at the time of the menopause and the occasional tendency to acromegalic changes further serve to indicate the implication of the pituitary.

Other objective changes at the climacteric are shrinkage of the uterus and atrophy of the vaginal wall. The latter gives rise to a characteristic change in the microscopic appearance of the cast-off cells in the vaginal fluid. Instead of the earlier picture made up of flat epithelial cells with few leucocytes, there are found many small, round cells interspersed with many leucocytes. The vaginal atrophy frequently gives rise to persistent itching In some cases the atrophy is followed by secondary overgrowth of the epithelium of the vagina and vulva known as *kraurosis*—a condition difficult to correct.

Other associated disorders of the menopause that are often experienced are "rheumatic" aches and pains of muscles and joints, anginoid chest pains, and functional disorders of the circulatory system.

In addition to the organic causes of the menopausal disturbances, psychological factors also may play an important role. Women are taught fcom girlhood on to expect trouble at the

"change of life," and often have a rather neurotic attitude toward it This consideration no doubt accounts for the fact that placebos and other sorts of psychotherapy or simple seda tives often give marked relief Much can be accomplished, in addition, however, by the judicious use of therapeutic measures to correct the underlying endocrine disturbances

In the *treatment* of menopausal symptoms some excellent clinicians have been impressed with the value of X rays admin istered to the anterior pituitary with a view to diminishing the secretion of gonadotropin Theoretically, the same result may be obtained by the use of sex hormones, and these have the additional advantage of substitution therapy

In the more severe cases, hypodermatic injections of one or other of the available estrogens are indicated as a first step Rather large doses—in the neighborhood of ten thousand rat units or more daily—seem to give the best results, though smaller doses are often effective It seems to make little differ ence what estrogen is used, hence price is the controlling factor (Sevringhaus) After the symptoms come under control the dosage can often be largely reduced or the hypodermic syringe can be laid aside and preparations that are potent by mouth substituted In the less severe cases, oral medication alone may suffice from the beginning About as good results can be obtained from androgens as from estrogens—a fact which sug gests that the most important influence of the medication is that upon the pituitary gland Often after the symptoms are alleviated medication can be suspended either permanently or for longer or shorter periods until new demands arise The treatments may have to be continued at intervals for several years

STERILITY

From the *foregoing* discussion of pregnancy the possible ways in which failure of that function—that is, sterility—may occur can largely be deduced For purposes of this discussion, mechanical factors—pelvic abnormalities other than ovarian,

whether due to developmental defects or to disease—may be disregarded Obviously, any condition that would prevent the ovum from reaching the uterus or that would block access of the spermatozoon to the ovum would render conception im possible We are concerned here particularly with endocrine abnormalities that prevent either conception or successful development of the fertilized ovum

It should be recognized at once that infertility is relative Numerous cases are on record of sterile matings in which both parties were subsequently proved to be capable of propagation There are now known to exist among nonsterile individuals all degrees of fertility from the lowest to the highest Not only does the grade of fertility vary from one individual to the next, but it may change from time to time in the same person, depending upon a variety of circumstances If both parties to a given marriage are highly fertile, pregnancy results promptly and repeatedly—often in spite of contraceptive measures If both are of mediocre fertility, conceptions are likely to be in frequent If both are of low fertility, the union will be sterile though neither party is individually absolutely infertile "Vari able fertility of this sort is nearly always a function of the sex cells In considering the causes of sterility, it is therefore neces sary to take into account all conditions that may lead to the production of relatively infertile ova or spermatozoa Chief among such conditions are three gonad underdevelopment, de pressed constitutional states, and endocrine failure" (Meaker)

Women are not uncommonly subjects of marked under development of the generative organs Actual persistence of infantile conditions does not often occur, but in many cases the stage of progress characteristic of the pre adult state persists The common cause of this failure of the final completing touch of development is inefficiency of either the pituitary or the thyroid at the hebetic epoch The period of stress having passed, the thyroid or pituitary imbalance commonly rights itself and, adult years having been reached, no further signs of hormone deficiency may be evident Nevertheless, the endocrine failure

at the critical period has marked the woman for life Commonly, the underdevelopment of the reproductive organs remains as a permanent handicap to fertility The ovaries either *fail entirely to produce sex cells or, at best, only occasionally* discharge ova capable of being fertilized In men, gross underdevelopment of the testes is uncommon, but Meaker believes that the elements in the glands from which the sex cells are produced do meet this mishap Accordingly, the spermatozoa that are produced are defective Such cases are not accounted for by any conditions detectably present in adult life and no known method of treatment is effective in remedying the difficulty

The production of vigorous sex cells—either male or female—is dependent upon a condition of good health Fertility is depressed, therefore, by any condition in either partner which lowers the general bodily tone A common example is a combination of mental strain and physical inactivity in case of persons whose work lays great demand on their nervous energy Defects of metabolism due to such causes as faulty diet or general unhygienic living lessen fertility An improper balance of the food elements may lead to poor cellular nutrition ever though the weight of the body as a whole is brought above the normal level by an excess of tissue fat A considerable number of obese, sterile women illustrate this abnormality, the cause of their lack of fecundity may be merely protein starvation and not endocrine deficiency as often believed In the analysis of a given case, these nonendocrine factors must be given their due weight

Endocrine failure at puberty is likely, as above stated, to give rise to sterility because of underdevelopment of the generative organs Having passed this critical period, however, the individual is still liable to sterilizing endocrine defects arising later in life It is probable that serious failure of any internal secretions will result in high degrees of infertility In Meaker's experience, the primary glandular defect in sterile women most commonly occurs in the anterior lobe of the pituitary

gland This abnormality is found six times as frequently as primary ovarian deficiency The thyroid occupies the middle ground Failure in its function was half as frequent as pituitary deficiency but was encountered three times as often as defective hormone production in the ovary

Sterility, then, may result from many causes Any single one of these may account for a given unfruitful mating More commonly, two or more causes are operative simultaneously and the correction of no one of them is likely to be satisfactorily effective, though the relative fertility may thereby be sufficiently improved to permit an occasional pregnancy Since the fault may lie in either partner, infertile matings rather than individual infertility should engage the attention of the physician In Meaker's records, there are numerous cases in which wives have been subjected to abdominal operations in the hope of correcting what was actually failure of sex cell production in their husbands It is only by adequate attention to the conditions in both partners that such blunders are to be forestalled

In *summary* we may say that the reproductive functions are perhaps more strikingly under endocrine control than are any other physiological activities In the first place, the hormones are necessary for the maintenance of a healthy body, in which alone can normal sexual development and functioning take place But, more directly, the internal secretions influence the reproductive processes themselves Not only do we have to consider the hormones of the gonads, but those of other endocrine glands as well These are probably all involved in bringing the individual to the stage of normal puberty at which the sex functions become active

In the male, with the onset of puberty, the testes undergo accelerated development and begin to produce spermatozoa Their structural and functional integrity from this time forth depends upon a normal supply of hormones and particularly of those from the thyroid, the pituitary, and the adrenal cortex Otherwise, they do not seem to be under special control

In the female, the sexual processes are cyclic. The periodicity is determined immediately by fluctuations in the production of the ovarian hormones, estrogen and progestin But the ovary is, in turn, controlled in large measure by the anterior lobe of the pituitary The period of reproductivity is ushered in by the discharge of an ovum from a graafian follicle, which likewise produces estrogen The estrogen stimulates the interior of the uterus—the endometrium—to preparatory changes looking to the reception of the fertilized ovum The uterine stimulation is continued by progestin, secreted from the corpus luteum that develops in the ruptured graafian follicle

If fertilization does not occur, the ovarian hormone tide ebbs and the endometrium reverts to its previous condition, the excess tissue being thrown off in the menstrual flow

If fertilization takes places, the condition of pregnancy begins by the fixation of the ovum through its chorionic envelope in the uterine wall The chorion and the endometrium in contact with it hypertrophy to form the placenta The corpus luteum persists and continues to secrete progestin as well as estrogen, both of which serve to aid the further development of the endometrium Soon after conception, the placenta also begins to contribute hormones which have regulatory effects on the processes that serve to promote the pregnancy

Under the influence of estrogen and progestin—and, perhaps, an anterior lobe hormone, mammotropin—the mammary glands enlarge and their secreting tissue markedly increases At about the time of the birth of the child, under the influence of a special hormone of the anterior lobe of the pituitary, prolactin, they begin to secrete milk

At about the forty seventh year, on the average, the reproductive activities of women come to an end in the condition known as the climacteric or menopause This is brought about primarily by failure of hormone production in the ovaries The state of glandular imbalance thereby set up leads temporarily to a more or less disagreeable train of symptoms in which nervous irritability is the chief manifestation

An inability to conceive and give birth to living young is known as sterility This may be due to lack of reproductive efficiency in either would be parent Infertility is relative It may result from any cause leading to ill health but is frequently due to endocrine deficiency There is evidence that the glands in their relative importance in this regard are the pituitary, the thyroid, and the gonads The gonads are reported to be at fault about one sixth as frequently as the pituitary

The use of gland products in the treatment of reproductive abnormalities is at times successful, but further research is needed to define their potentialities and limitations

REFERENCES

See chapters on the sex glands

XII. HORMONE REGULATION OF THE DIGESTIVE FUNCTIONS

THE DIGESTIVE system consists fundamentally of a long tube through which the food is passed At various way stations the food receives a variety of chemical treatments by which it is broken down into simpler substances that can be absorbed and carried to the tissues for their nourishment A brief review of the outstanding facts of the physiology of digestion may aid in an understanding of the pertinent endocrinology

The digestive activities are chiefly of three sorts The process of secretion in a variety of glands affords the digestive juices By another kind of activity, the motor functions, the food mass is mixed and moved along the tract Finally, by the process of absorption, the digested food is transferred into the blood stream Conventionally a fourth phase of digestion, the mechanical disruption of the food substances into small particles, is catalogued, but this is only a special aspect of the motor functions

In the mouth, the teeth begin the process of attrition of the food The secretion of the salivary glands is added This serves to begin the chemical changes of starches to sugar and acts as a lubricant to facilitate swallowing The chewing process, so far as we know, is not subject to any hormone control It is regulated by nerve impulses, either volitional or reflex After the food leaves the mouth the processes to which it is exposed are completely involuntary, except that the final ejection of undigested residue is partly volitional

In the stomach, pepsin and hydrochloric acid are secreted by glands in the wall of that organ The upper part of the stomach serves merely as a quiescent reservoir, but at the lower end the food is churned by a series of waves whereby the digestive juices are thoroughly mixed with it It is then passed on to the small intestines Here the secretion of the pancreas and bile from the liver are added The mixing continues and the mass is gradually propelled into the colon Absorption, at least of accessory substances such as alcohol or drugs, begins to a slight degree in the stomach and proceeds throughout the length of the small intestine but is completed in the colon The undigested residues are passed periodically into the lower or rectal segment of the tract from which evacuation finally takes place

Beginning with the salivary glands, the various portions of the digestive system are under double *nervous control* This is exercised by the involuntary, or autonomic, nervous system It consists, in general, of two opposing portions, the *sympathetic* and the *parasympathetic* As pertaining to digestion, the sympathetic system, by and large, serves to retard activities whereas the parasympathetic augments them From the standpoint of endocrinology, the sympathetic system demands special attention because of the close relationship existing between it and the medulla of the adrenal glands Since the sympathetic mechanism is specially subject to the action of adrenine, the suggestion has been offered that some one or more of the other hormones has a special relationship to the parasympathetic system As will be mentioned later, there is some evidence that insulin from the pancreas may serve such a purpose, but the conception is attractive rather more as a possible example of the orderliness of nature than as a well substantiated aspect of physiology

HORMONES AND APPETITE

There is evidence that hormone control of nutrition may begin even in advance of the actual taking of food Richter has

shown that the condition of the endocrine glands of experimental animals to a considerable extent determines what they spontaneously consume Thus, when parathyroid deficiency is set up by removal of the glands, the animals develop an avidity for calcium solution and thus serve as their own physicians Similarly, adrenal deficiency leads to increased appetite for the salt that is needed for survival The use of insulin for the improvement of the nutrition of human patients may also rest on a similar effect of the hormone on the appetite rather than on the hunger mechanism, as earlier believed Years ago, Davis showed that malnourished babies, given a choice of numerous foods, would select those needed to restore their health The choices often seemed at strange variance with those that an experienced pediatrician would have made How the babies sensed what they needed has remained a puzzle Perhaps the basis was something akin to that of Richter's rats—a selective influence of needs on appetites To what extent in human experience the hormone titers of the blood may have a regulatory influence upon cravings for this or that food is an interesting and unsolved problem

SALIVARY GLANDS

The control of salivary secretion varies from one species to another In some animals the stimulatory impulses are supplied mostly by the sympathetic system and in others by the parasympathetic. In most animals, however, the injection of adrenine serves to evoke some, if not copious, secretion, hence, sympathetic control is perhaps predominant

The special relationship between the emotions and the outpouring of secretion from the adrenals was discussed at length in the chapter on those glands Anyone who has found himself undertaking to make a public speech with his tongue cleaving to the roof of his mouth needs no further proof that the emotions—therefore the sympathetic system—have also an inhibitory effect upon salivary output The final details as to

whether and when adrenine causes the one effect and when the other have not been determined

Posterior lobe pituitary extract in larges doses has been shown to check salivary secretion, but this is probably not a matter of physiologic interest, there is no reason to suppose that the hormone is ever discharged, naturally, in sufficient amount to produce this effect

The thyroid gland, on the other hand, no doubt does play a part, if only indirectly, in regulating this function An excess of thyroid hormone causes an increase in the sensitiveness of both components of the autonomic system This increase has been cited to explain the fact that often, in clinical hyperthyroidism in man, copious salivary flow can be set up by relatively weak stimuli

On theoretical grounds, insulin might also be expected to have a significant influence, but the problem apparently has received little study Of the other theoretical possibilities too little is known to justify further discussion Altogether, the evidence seems to indicate that, except under conditions of emotional stress in which adrenine may play a part, the salivary secretion is normally little influenced by hormones

A few words in passing may be said of the salivary glands as themselves organs of internal secretion At various times in the past, evidence has been published that purported to demonstrate such a function Suffice it here to state that physiologists have remained unconvinced that any of this evidence is valid

STOMACH

When food is first taken into the stomach, secretory activity is set up through the agency of a nervous mechanism In a hungry subject, the taste or even the mere sight of attractive food causes not only the mouth to water but the stomach also This latter outpouring is known as the "appetite juice" The food remains in the stomach normally about four hours but, according to the best of the evidence, the nervous secretion lasts only

about fifteen minutes (Carlson) Secretion during the remainder of the period is under chemical control

Is the chemical stimulant a hormone? On a priori grounds this need not be postulated The digestive products themselves might stimulate the secretion Indeed, a variety of food derivatives, the so-called *secretagogues*, have been shown to act in this way The secretagogues might serve to stimulate the gastric glands directly But they likewise might produce their effect by causing the secretion of stimulating hormones The problem is intricate and has not yet been fully solved It can now be dogmatically stated, though, that, in part at least, the mechanism involved is hormone production

First of all, secretagogues are effective when the nerve supply to the stomach has been cut This rules out ordinary reflex activity But the stomach is well supplied with a nervous system of its own—the "myenteric plexus" The secretagogues might act by stimulating this system, thus setting up local reflexes The problem could be answered only by direct research This was undertaken by Edkins in 1906 He first introduced into the stomach about two ounces of weak salt solution—a substance having little or no stimulating effect When the organ was emptied at the end of an hour, it was found that none of the fluid had been absorbed nor had any digestive secretion been added This served as the control observation Then he repeated the procedure, but in the interim between introducing and withdrawing the fluid from the stomach he injected one or other of the secretagogues into the blood stream This had no influence on gastric secretion The conclusion followed that the secretagogues do not themselves act as hormones Again repeating the experiment, he injected into the blood an extract made from scrapings of the stomach lining This did cause an outpouring of gastric juice Hence the conclusion—at first thought most surprising—was that the actual stimulating substance is something found in the stomach cells The secretagogues, then, cause a flow of gastric juice by arousing hormone production

The active principle in the effective extract Edkins called *gastrin* The observations have since been confirmed by numerous other investigators Without recounting the various technical procedures that were necessary to rule out experimental error, we may simply state that during the process of digestion, under the influence of secretagogues, the stomach cells form a hormone, gastrin This is absorbed by the blood stream and distributed throughout the body That part of it which finally gets back to the stomach stimulates the secreting cells and gastric juice is poured out According to Ivy, the various other hormones that have been discussed in preceding chapters exert no significant influence upon gastric secretion directly, though the stomach may share in the general bodily disorders that result when normal hormone supplies are interfered with

The work of Ivy and of Lim and their associates indicates that the stomach is subject to inhibition as well as to stimulation by hormonal agents From the mucous lining of the upper intestine they have derived a purified material designated *enterogastrone*, which brings the secretion of gastric juice partly or wholly to a standstill The same or a similar substance, *urogastrone*, is obtainable also from urine

So much for gastric secretion Little is known regarding hormone influences on the motor function Many years ago, Cannon showed that emotional excitement brings the movements of the stomach to a standstill Adrenal discharge is a common accompaniment of emotions Presumably, therefore, adrenine does play a part—an inhibitory part—under emergency conditions According to Ivy, the injection of adrenine alone without accompanying emotional excitation has no consistent effect of this sort, though Cannon's experience has been rather to the contrary Of recent years insulin has been frequently reported to increase hunger The sensation of hunger is due to exaggerated motor activity in the stomach Direct experimentation, however, in which the motor activities were graphically registered, has failed to bear out very satisfactorily the supposition that insulin plays a significant role in this regard

THE PANCREAS

One of the landmarks in the development of endocrinology was the discovery by Bayliss and Starling of the hormone control of pancreatic secretion Indeed, it was in the description of their work that the word "hormone" was first used The investigation started with the well known fact that the introduction of weak acid into the upper part of the intestine causes the pancreas to pour out its characteristic secretion It was found that when all nerves to this part of the tract, the *duodenum*, were cut the reaction was not interfered with Proceeding much as did Edkins—whose technic was actually an adaptation of that of Bayliss and Starling who really preceded him—these authors scraped off the mucous membrance of the duodenum and ground it in a mortar with weak hydrochloric acid The material was boiled to coagulate the protein in it, then it was nearly neutralized with an alkali and injected into the blood stream A copious flow of pancreatic juice followed This was true whether the nerve supply to the gland was intact or destroyed The next stage in the research was to prove that the flow was not due merely to dilatation of the blood vessels of the gland, an effect that can be obtained with a variety of tissue extracts To meet this objection they further purified the extract until they were able to obtain the pancreatic flow without significant changes in the circulation The active substance they named *secretin* It was further found, however, that extraction of the intestinal mucous membrane with ordinary weak salt solution—imitation blood serum—would not give a significant yield of secretin Hence, the deduction was drawn that this substance exists in the epithelial cells, not as secretin—which is soluble in water—but as a preformed material from which secretin is produced by the action of acid This precursor was called *prosecretin*

In 1934, Agren succeeded in obtaining secretin in crystalline form It contains sulphur, arginine, histidine, and some lysine It gives some, but not all, the tests for protein and is

digested by protein splitting enzymes, hence is to be regarded as a special type of protein When given to experimental animals by vein, the pure secretin causes secretion from the pancreas, the liver, and the intestinal glands—has, in short, a "generalized intestinal diuretic" effect It has been found to have no influence on insulin output, on blood pressure, on the gall bladder, or on intestinal motility, as do some of the less pure preparations

The various conditions that had to be met to produce an active preparation of secretin are found normally in the alimentary tract When the food is discharged from the stomach it contains a weak solution of hydrochloric acid In the duodenum it comes in contact with the cells that produce prosecretin Nevertheless, such experiments do not prove the actual existence of secretin in the circulating blood, the condition which is postulated in the definition of a hormone Final proof of its being a true hormone had to be secured experimentally This has been accomplished by a special method whereby two dogs were used as a sort of team Into the veins of one, the recipient, blood was injected that had been obtained from the other, the donor, into whose duodenum weak acid had previously been introduced The blood of the donor caused an active secretion from the pancreas of the recipient, a fact which proved that the stimulating substance was a genuine internal secretion

THE LIVER

Various observers have noted that the injection of extracts containing secretin produce an increased flow of bile from the liver as well as of pancreatic juice Since, in general, these two substances normally appear in the intestines at the same time and under the same conditions, it might be assumed a priori that the liver would actually share in the response to secretin That it does so has been both affirmed and denied The more recent work of Agren with crystalline secretin would seem to have settled the controversy in the affirmative

Dragstedt and associates have reported (1938) that the fat metabolism of the liver is under special hormone control Their evidence, in brief, is that in experimental diabetes the liver accumulates fat in injurious proportions The giving of insulin fails to protect the animals from this mishap, but feeding raw pancreas does do so By alcoholic extraction and purification, the actual agent having this property has been obtained in such potency that one gram a day suffices for protection The product is known as *lipocaic*

To a considerable extent, the bile that is secreted by the liver is stored in the gall bladder to be ejected periodically as needed This structure has been shown to be under separate control by a special hormone which Ivy has called *cholecystokinin* ("gall bladder mover") It is obtained, as is secretin, from the mucous membrane of the upper part of the intestine and, to a slight extent, from that of the stomach It occurs in extracts made in various ways to contain secretin and has been thought by a number of investigators to be identical with that hormone Ivy and his collaborators, however, have been able to prepare active secretin solutions that have no effect on the gall bladder, and active cholecystokinin that has no effect on the pancreas

THE INTESTINES

Digestion in the intestines is carried on not only by bile and pancreatic juice, but with the further aid of secretions from the mucous membrane of this part of the tract itself Since the production of the intestinal juice is a primitive sort of function such as those that are pre eminently under hormone influence, such control might be anticipated here Agren's results with pure secretin indicate that such is, indeed, the case Furthermore, Nasset has prepared another intestine stimulating material, *enterocrinin*, which appears to have the attributes of a true hormone It, like secretin, is derived from the mucous lining of the small and large intestines Since it does not excite the pancreas, it cannot be regarded as identical with secretin

The process of absorption takes place almost entirely from the intestines Little is known as to how this function is con trolled, whether by hormone mechanism or otherwise Pos sibly nothing more than adequate local circulation is needed to this end

Whether the motor functions are under hormone regulation has been investigated and debated many times What was said in the preceding paragraphs regarding the motility of the stomach largely applies also to the intestines Any glandular disturbance sufficient to cause ill health is likely to find reper cussion in their functions Excessive thyroid secretion is often accompanied by diarrhea, stubborn constipation is a character istic symptom of thyroid deficiency It would seem probable, therefore, that the thyroid hormone normally exerts a con trolling influence Adrenal deficiency is marked by a tendency to diarrhea, and it has long been known from Cannon's work that an emotional disturbance with its attendant discharge of adrenine characteristically leads to intestinal standstill This latter fact probably indicates that the adrenine, too, serves to some extent as a normal controlling substance—in so far as emergencies may be included in the category of the normal The evidence, however, is equivocal in that, as is well known, emotions may likewise cause diarrhea

To *summarize*, several hormones are now known that have specifically to do with gastrointestinal functions The mucous lining of the stomach forms gastrin which is an important stimulant to the secretion of gastric juice The intestine forms the inhibitory hormone, enterogastrone The lower part of the stomach, but more especially the upper part of the intestine, supplies the hormone, secretin, which shares importantly with the nervous system in the control of the secretion of pancreatic juice as well as bile and intestinal juice The last named func tion is shared by enterocrinin From the intestinal mucosa can be obtained also the hormone, cholecystokinin, that serves to cause contraction of the gall bladder and thus the ejection of bile into the upper intestine during the progress of digestion

From the pancreas is derived lipocaic, which influences fat metabolism in the liver There is substantial evidence that adrenine is discharged from the adrenal glands in sufficient amount to play a significant role in conjunction with the sympathetic system in bringing about quiescence of the gastrointestinal tract when the individual is integrated for meeting emergencies The thyroid hormone, perhaps, has a normal part in the regulation of the motor activity of at least the lower bowel There is some, though not very satisfactory, evidence that the pancreatic hormone, insulin, may promote gastrointestinal activity The other internal secretions are not known to have any normal influence on the functions of the digestive tract except as they serve to promote general bodily health

XIII. INSULIN AND DIABETES

SELDOM DOES science—medical science in particular—advance in perfectly straight lines or by perfectly logical steps one directly above the other In ascending the mountain of knowledge, as in ascending physical mountains, progress more often is accomplished by a zigzag course At times, a mountain trail may seem to have lost the habit of ascending, it may even recede toward lower levels And it is only by patiently threading one's way through obscuring growths at the base of the mountain, and then oftimes after further baffling experiences in fogs about the higher levels, that one emerges finally to the clearer view and the immediate consciousness of achievement" With these words, Murlin prefaces a story of the discovery of insulin The story is worth recounting in some detail both for its own sake and for the light it throws upon the ways of scientists at their everyday work

The first known recognition of diabetes, according to Allen, occurred at about the time when Rome was at the height of its power The disorder was discussed by Celsus (30 B C–50 A D) Aretaeus of Cappadocia, who was a contemporary of Nero (30–90 A D), wrote

> Diabetes is a strange disease, which fortunately is not very frequent It consists in the flesh and bones running together into urine It is like dropsy in that the cause of both is moisture and coldness but in diabetes the moisture escapes through the kidneys and bladder The illness develops very slowly Its final outcome is death The emaciation increases very rapidly, so that the existence

of the patients is a sad and painful one The patients are tortured by an unquenchable thirst, they never cease drinking and urinating, and the quantity of the urine exceeds that of the liquid imbibed If he abstains only a short time his mouth becomes parched, and he feels as if a consuming fire were raging in his bowels The disease was called diabetes, as though it were a siphon ("Diabetes" is the Greek word for siphon), because it converts the human body into a pipe for the transflux of liquid humors Now, since the patient goes on drinking and urinating, while only the smallest portion of what he drinks is assimilated by the body, life naturally cannot be preserved very long, for a portion of the flesh is also excreted through the urine The cause of the disease may be that some malignity has been left in the system by some acute malady, which afterward is developed into this disease It is possible also that it is caused by a poison contained in the kidneys or bladder, or by the bite of the thirst adder or dipsas (Quoted from Allen)

Aretaeus apparently regarded diabetes as a disease of the stomach, but late observers were more inclined to attribute it to disordered functioning of the kidneys, an idea that still persists among many of the laity

The earlier accounts stressed especially the copiousness of urinary output Later the emphasis was shifted somewhat to include the abnormality that is even more characteristic than the exaggerated fluid excretion, namely, the sweetness of the urine The disease we are discussing, diabetes mellitus, is differentiated from another disorder, diabetes insipidus, by this quality The earliest mention of the sweetness of the urine seems to have been made by a writer in India in the sixth century He gave the disease the name *Madhumeha*, or honey urine The adjective "mellitus" in the English name of the disorder carries precisely the same significance (Greek *meli*, honey)

In the intervening years numerous writers discussed the disease, descriptively and speculatively, but nothing was learned of its real cause until about half a century ago Such experi

mental study as had been made in attempts to solve the problem had been mostly directed toward the liver, which was known to play a special role in carbohydrate metabolism Claude Bernard's classic researches on this organ were, indeed, motivated in part by a desire to clear up the mystery of diabetes

As has frequently happened in science, the first important *observation was actually a by product of a research designed* for a different purpose—another example of "chance favoring the prepared mind" The German investigators Minkowski and von Mehring were interested in the study of the pancreas in relation to digestion It is said that the first actual important step in the discovery of the relationship of this gland to diabetes was made by a humble attendant who was caring for the experimental animals of the doctors He noted that the urine of dogs that were suffering from deprivation of the pancreas was attracting great swarms of flies This curious happening was called to the attention of one of the investigators, whereupon a chemical test of the urine was made It was found to be loaded with sugar Thus, experimental diabetes had unwittingly been produced and the problem was now open to intensive investigation

The significance of the new discovery was instantly recognized and high hopes were entertained that the age-old mystery was at last to be solved The day of salvation for the diabetic was at hand At this time the medical world was athrill at the therapeutic marvel of the day, the thyroid cure of myxedema Now diabetes was shown to be due to pancreatic deficiency Would it not similarly yield to pancreatic extract, or even to simple pancreas feeding?

But to quote again from Murlin

> The Minkowski contribution got us only out of the woods, we were still a long way from the summit and apparently insurmountable barriers interposed There were not wanting many who caught, or thought they caught, glimpses of a sure passage over the difficulties But many of these glimpses proved wholly illusory,

most of the passages had to be abandoned completely As in mountain climbing, so in scientific pioneering the surest progress often is made by *following up as far as it goes a trail blazed by somebody* else Failures may show up along the way, mistakes which appear utterly foolish in the light of newer experience This one has gone off on the wrong branch, that one has followed a false lead But eventually comes along a bolder spirit or one of surer instinct, or, it may be by pure chance, the new wayfarer hits upon the right clue and amazingly and triumphantly he leads the way toward the summit

The details of the work of Minkowski were not published until 1892 He fully sensed the significance of the discovery and tried to make an extract of dog's pancreas that would have a beneficial effect on the experimental diabetes he had produced, but without success Another experimenter, however, Caparelli, had slightly anticipated him in this application of the discovery and had had somewhat better fortune A simple saline extract of pancreas was injected into the body cavity of a dog having diabetes There followed a marked lessening, or even complete disappearance, of sugar from the urine

As was inevitable, alert clinicians immediately attempted to use the new knowledge without awaiting the slow progress of physiology toward the solution of their problem Men were dying of diabetes and any straw of hope had to be grasped Some administered fresh pancreas by mouth, some gave juice expressed from the gland, and some administered extracts Both successes and failures were early reported Pancreas had long been used as a food—under the name "sweetbreads" No relationship between the use of that viand and the condition of diabetics had been noted As might perhaps have been anticipated—certainly as hindsight now makes abundantly clear—no simple solution of the problem was to be hoped for Bormann, nevertheless, administered roast pancreas by mouth, later infusions by rectum, and finally subcutaneous injections of raw pancreas extract One of his patients who received the

latter treatment gained eight pounds in six weeks and the torch of hope glowed more brightly Mostly, however, the results were negative—or worse In 1896 came a report from Russia of two other patients who gained six and ten pounds, respectively, from the administration of watery extracts of fresh pancreas administered by rectal infusion Considering the fact that such extracts of pancreas contain digestive enzymes in fairly large amounts, it is not to be wondered at that the patients could not long tolerate the treatment

Again, in 1897, favorable results were reported in human cases from feeding raw pancreas or a glycerine extract of that organ The treatment, however, soon became repugnant to the patients In this same year a careful piece of research upon dogs was published The French investigators, Hougounenq and Doyon, made extracts in a variety of ways and administered them by stomach They were unable to demonstrate any beneficial effects These negative results were impressive and to a considerable extent discouraged physicians from further therapeutic experiments along this line

A year later the problem was nearly solved Blumenthal squeezed the juice from raw pancreas and treated it with alcohol to remove the protein When administered by vein the extract killed his experimental animals, and when injected subcutaneously caused ulcers in both animals and men severely afflicted with diabetes In retrospect, it is apparent that Blumenthal was actually using a crude preparation of insulin Indeed, in one case he was able to increase the utilization of sugar by 40 per cent Had the side effects been less severe, it is not improbable that this investigator would have gone on to the success that was finally achieved a quarter of a century later

The next ten years were barren as far as therapeutic results were concerned But under the microscope more and more evidence was being seen that in human diabetes the pancreas is truly the organ at fault In a high proportion of autopsies of patients dying of that disease, destructive changes in the pan

One of the first cases of diabetes in which insulin was used The first picture shows the patient on Dec 7, 19[illegible], two years after the onset of the disease The second shows the same boy after treatment, on Feb [illegible]6, 192[illegible] His weight had increased from 1[illegible] to [illegible]0 pounds Courtesy of Dr Ralph H Major Case reported in Jour Am Med Assn 80 159[illegible] 19[illegible]

creatic *islands of Langerhans* were shown to occur As will be discussed later, these "islands" are the source of insulin

The next outstanding contribution was made by Zuelzer in 1908 Minkowski's work had led to a famous controversy be tween him and the eminent physiologist Pflueger This latter investigator had laid down the principle that a function of hormone production cannot be proved by extirpation experi ments alone It is necessary, he maintained, to show also that the symptoms following the extirpation can be alleviated by ad ministering preparations of the missing gland Guided by this principle and believing that previous failures might have been due to the condition of the pancreatic tissue from which the ex tracts were made, Zuelzer concentrated attention upon the use of very fresh material He was all but successful He collected glands from animals at the height of digestion and extracted them to remove the formed enzymes He next pressed out the juice and treated it with alcohol with the aim of precipitating the proteins The material was then freed from the alcohol and injected either subcutaneously or by vein In dogs rendered diabetic by surgical removal of the pancreas, the sugar output in the urine was nearly or completely stopped Eight human patients were treated Several showed definite improvement as regards the sugar loss One became entirely free of sugar in spite of the fact that he ate a considerable amount of bread, the beneficial effect persisted for four days A boy of six re ceived a single injection of five cubic centimeters (about a half teaspoonful) of the extract by vein The sugar in the urine was decreased by half and his symptoms otherwise improved He showed, however, a marked fever and was severely nause ated Zuelzer then engaged in further attempts to purify his extract and by 1912 had sufficiently succeeded to obtain a patent for the preparation under the name "Ascomatol" Further studies were continued with Reuter until the outbreak of the World War in 1914, at which time a product had been obtained which lowered the blood sugar "as much as desired"

From the results of these various trials and errors, a signifi

cant principle was gradually being sensed The presence of digestive enzymes in the pancreatic products was a major source of difficulty Recognizing this principle, Scott, in 1911, undertook to secure an extract of the islands of Langerhans themselves, in which, there was now substantial reason to believe, the effective hormone was to be found He made use of an old observation that if the ducts leading from the pancreas are ligated, that part of the glandular tissue which has to do with enzyme formation atropies, leaving the islands of Langerhans behind Scott had the misfortune to fail to get the ducts completely ligated, hence he did not secure the atrophy he desired Having failed in that endeavor, he then attempted to do away with the troublesome enzymes by treating the extract with alcohol This was the same method that his predecessors had used—but with the end in view of freeing the extract from protein The product that Scott obtained so lowered the blood pressure as not to be very serviceable As will be noted from the denouement of the story, Scott, too, barely missed the trail

The next important approach to success was made by the eminent scientist Starling, whose monumental contribution on secretin was recounted in the previous chapter He worked with Knowlton, investigating the possibility that the illusive antidiabetic hormone could be captured by the same method that had proved successful in the case of secretin An extract of pancreas was made in acid solution and administered to a dog Actually, the classic Starling heart lung preparation was used, that is, by tying the peoper blood vessels the circulation was confined to the heart and the lungs, the rest of the body being sacrificed It was shown that the acid solution enabled the heart of a diabetic dog to utilize sugar This result was at once independently confirmed But seeking with Patterson to verify it in a third attempt, Starling failed He thereupon drew the mistaken conclusion that his previous experiment with Knowlton had been defective During this period, Kleiner and Meltzer made a preliminary report, succeeded by a fuller account in 1919, showing again that pancreatic extract caused a

decrease in blood sugar and usually in urine sugar The possibility of using such extract clinically was suggested

Having read the report of Knowlton and Starling, which confirmed in a measure one of his own previous experiments, Murlin also entered the lists In collaboration with Kramer, he prepared an extract but used stronger acid than had the previous investigators This was neutralized and boiled When injected into the vein of a diabetic dog the extract caused the urine to become sugar free in a little more than two hours and to remain so for six hours But this time the dog's own liver apparently tricked the investigators It would seem that during the sugar free interval that organ stored up a considerable amount of glycogen, and when the effect of the extract had worn off this stored carbohydrate was poured out as urine sugar and the net gain was nil Nevertheless, Murlin carried on, as opportunity offered, for the next three years and got results that convinced him that he was hot upon the trail of the hormone The first World War then interrupted his work, as it had Zuelzer's, and he discontinued his researches to take part in the military service In the fall of 1921 the work was resumed, using methods which, in principle, were closely similar to those that in the next few months proved successful

Fate now at long last relented and the final step was taken A young Canadian physician, Banting, recently returned from service in the war, happened to read in a medical journal an article describing the old experiment of ligating the pancreatic ducts It occurred to him, as it had to Scott, that the troublesome enzyme factor in pancreas extracts might be circumvented by the use of this technic He decided once more to put the idea to practical test He arranged to work in the laboratory of Macleod at the University of Toronto Here he was given the assistance of Best, who was then a junior medical student With fine enthusiasm they went at the job of preparing the experimental animals The investigators literally lived in the laboratory day and night Soon arose the problems of the preparation and refinement of extracts of the pancreatic tissue Collip was

then added to the group and brought to bear the experience gained in several years of devotion to this type of chemistry

As a matter of fact, the use of Langerhans tissue from atrophic glands soon proved to be impracticable—the yield was very small—and other means were sought to produce extracts which were at once sufficiently potent to be effective and sufficiently pure not to cause unpleasant or dangerous by-symptoms The fact was abundantly confirmed that it was the enzyme, trypsin, in the extracts that had to be guarded against Unless this was destroyed, it simply digested the insulin and reduced the yield to insignificant amounts Some success was attained by using glands at the fetal stage of development before trypsin formation had begun As experience accumulated, the possibility was at last realized of using ordinary beef glands but, by the adroit employment of alcohol and of acid in the extraction processes, to circumvent the enzyme action It was primarily Collip to whom the credit belongs for having so improved upon the methods of Scott that practical success was finally achieved The resulting extract in concentrated form was first given to the investigators themselves, to make sure that it was not harmful Its use in the treatment of human diabetes was then begun, in January, 1922 By February 22, it had been tried with hopeful results in seven cases Schafer had previously—in 1916—suggested the name *insulin* for the active principle of the pancreas and this name the Canadian investigators adopted The discovery was then announced

The remainder of the story can never adequately be told Insulin came immediately into wide use the world over, and in the years that have elapsed since it became available it has brought new hope and comfort and has added to the years of life of thousands of human beings

Shall we attempt to apportion the glory won? Almost never does a scientific discovery spring at once "full panoplied from the brow of Jove" With rare exception, it is but the last step in a winding trail How much acclaim should go to the nameless attendant of Minkowski who actually made perhaps the

most fundamental of all the observations recorded? How much to the savants who promptly sensed the significance of the clue and made the first experiments that pointed the direction of the trail? To each of these men and to their successors—even those who only closed off blind passages—our thanks are due. Finally, what thanks shall we render to the dogs whose graves serve as silent milestones in the long ascent of the trail? The many experiments were made almost exclusively on these animals and, for technical reasons, no other animals would have served so well, if at all. Perhaps, but for their aid the discovery would still lie in the future and an aggregate of many thousands of years of human life would already have paid the penalty of continued ignorance.

CHEMISTRY OF INSULIN

As early as 1927, Abel and coworkers had succeeded in purifying insulin to the point at which it was obtained in crystalline form. It was found by this group, and confirmed by subsequent workers, that the purified material is a sulphur containing protein. When broken down chemically it yields, as do other proteins, several amino acids including cystein, tyrosin, glutamic acid, leucine, histidine, and lysine. As shown by its molecular weight of about thirty five thousand, it is a relatively small aggregate—for a protein. When injected, it is absorbed and transported with corresponding rapidity. The question has been raised whether the insulin of the chemist represents the true hormone as secreted or whether it is merely a split-off, rapidly acting fraction of the natural molecule. To promote a more steady input for clinical purposes, insulin may be combined with other materials to form more stable compounds. Both zinc and histamine are used commercially for this purpose.

To facilitate assaying, the Standardization Committee of the League of Nations has defined a "unit" of insulin as one third of that amount which serves in three hours to reduce the blood

sugar of the test animal (two kilogram rabbit) to a level that will bring about convulsions The standard preparation contains eight units per milligram (about five hundred units per grain)

THE PANCREAS AS AN ENDOCRINE GLAND

The pancreas was known as a digestive gland long before its relationship to diabetes was even suspected It pours into the alimentary tract a juice that contains three important enzymes that aid in the splitting respectively of protein, carbohydrate, and fat These enzymes are produced in a mass of glandular tissue which in structure rather closely resembles that of the salivary glands Interspersed among the lobules of the glandular tissue are numerous inclusions, the so-called islands of Langerhans Since it is these from which insulin is derived they alone need concern us here

The *islands of Langerhans* first make their appearance in human embryos when they are about two inches in length The pancreas arises as an outgrowth from the primitive intestine, the sprout branching to form a treelike structure with the glandular epithelium representing the ultimate twigs The intermediate stems are the tubules through which the secretion collects in the main ducts The islands arise as outgrowths of the primitive gland tubules At first, they consist of solid clusters of cells—a dozen or more in each island Blood vessels make their way into the cell masses, which then enlarge somewhat Throughout life there is evidence to believe new glands continue to be slowly produced as outgrowths from the duct epithelium Three different types of cells have been described as making up the adult islands, but since their respective functions are not clearly known they need not, as such, concern us further

Islands of Langerhans, or structures that resemble them, are found in all vertebrates from fishes up to man They differ considerably in relative size and number In fishes, the island tissue constitutes but a single mass

PANCREATIC DEFICIENCY—HYPOINSULINISM

The fact was previously noted that regressive changes in the islands are characteristic findings in subjects of diabetes mellitus Indeed, pancreatic degeneration in association with that disease had been observed a century ago, but its significance was not apprehended Whether insulin deficiency arises as a result of disease or is produced experimentally by extirpation of the pancreas, the results are similar

The feature that is best known to the laity is the one previously discussed, namely, the occurrence of sugar in the urine (*glycosuria*) This, however, is but a superficial manifestation of a deep-seated alteration of metabolism The first change that can be detected as lying behind the glycosuria is a sweeping out of the *glycogen* (stored carbohydrate) of the liver For some reason not yet understood, the glycogen supply of the muscles may remain intact and indeed, according to Macleod, that of the heart muscle may even increase Not only is the liver glycogen depleted, but that organ loses its ability to replenish its store

The liver supply having been exhausted, the body turns to other tissue substances that can be converted so that the tissues come to melt away into sugar All the symptoms of acute starvation arise and these are associated with certain others that are possibly due directly to the excess of sugar with which the body is flooded Literally, the individual tissue cells starve in the midst of plenty

In so far as the body proteins are being utilized for conversion into sugar, the result—except for tissue loss—is not serious When, however, the fat is drawn upon, the processes of oxidation cannot keep pace with the breakdown and partially burned fat derivatives, the so-called *ketone bodies*, make their appearance in the blood and then in the urine One of these is the well known substance acetone, which is volatile and can, therefore, partly be thrown off in the breath, to which it gives a peculiar sweetish odor

Of special technical importance is another abnormality of metabolism that quickly becomes evident, namely, a change in the *respiratory quotient* When sugar and protein are being burned, as much carbon dioxide is produced, molecule for molecule, as oxygen is consumed The ratio of the two gases—in laboratory shorthand, the "R Q"—is one to-one, i e, 1 0 Fat, on the other hand, contains relatively more carbon than does sugar, and when it is being burned the R Q falls In absolute pancreatic deficiency, when the ability to burn carbohydrate has been completely lost, the R Q drops to 0 7

As would be assumed from the foregoing statements, the body loses weight The hungry tissues continue to demand food, though how the demand is actually expressed is not known More and more tissue is converted into sugar and this, in part, overflows into the blood Like any other blood constituent that occurs in excess, the sugar influences the kidney cells not only to throw off this excess, but also the water in which it is dissolved Thus arises another cardinal symptom of diabetes, excessive urine output, i e, *polyuria*

Many volumes have been written upon the clinical aspects of diabetes Space serves for mention here of only a few of the other characteristics In man, the disease ordinarily develops insidiously and in the beginning may produce no symptoms whatever In this early stage the disorder is often first detected when the individual applies for life insurance and sugar is found in the urine Then, as the condition progresses, the inability to burn sugar reaches a stage at which symptoms arise that the patient himself can recognize These commonly include excessive urine output which, in turn, leads to excessive thirst, increased appetite, progressive loss of weight, dryness in the mouth, and a feeling of lassitude followed by more and more trying general weakness Unless treatment is instituted, the patient is finally incapacitated for work In the eyes, cataracts or disturbances in the circulation of the retina are likely to occur Shooting pains in various parts of the body are often complained of Sexual impotence in men and menstrual dis

turbances in women are common Frequently boils occur to torment the patient and he is likely, finally, to be brought by persistent general or localized pruritus (itching) to an unhappy state surpassing even that of Job

At first, the patient is able to utilize a certain proportion of his carbohydrate food, but as the disease progresses the tolerance becomes less and less As he becomes more and more dependent upon fat as a source of energy, the ketone (acid) bodies increasingly accumulate This leads to the well known complication of diabetes technically known as *acidosis*—the condition that arises when the alkali reserves of the body are seriously depleted Unless the process is arrested, the patient typically becomes so intoxicated by acid as to lapse into unconsciousness (*coma*) and the tragedy ends in death

The treatment of diabetes in general is a threefold undertaking First, the need for food is restricted as much as is feasible by the limitation of bodily activity Next, the food is so selected as to furnish the elements that can most readily be utilized For this purpose some physicians prefer to make up the necessary calories largely from fat, others rely especially upon protein feeding (Richter's finding that diabetic rats develop a special appetite for fats supports the idea of those who, on a basis of clinical experience, prescribe high fat diets) Nearly all agree in the desirability of limiting the carbohydrate. As much as possible is accomplished by such management, the physician then administers enough insulin to permit the combustion of sufficient carbohydrate to complete the caloric quota The maintenance of somewhat less than average body weight is regarded by some physicians as desirable

Much has been written about the relationship of obesity to diabetes That fat people are especially liable to the disease is unquestioned, but the explanation of the fact is uncertain Perhaps the best surmise is that it is the excessive appetite of the patient which lies behind both phenomena More food is eaten than is used and the excess is laid down as fat Overconsumption at the same time puts a strain on the islands of Langerhans

to produce enough insulin to deal with the plethora of supplies Ultimately, the islands succumb to the strain and diabetes develops This theory presupposes that the islands initially are of less than normal vitality, however, because certain it is that many people endure obesity even of high degree for years without acquiring diabetes

Does insulin ever cure diabetes? In many cases it does so only in the sense that food cures hunger The need for the hormone continues to arise and as regularly must be met Theoretically, the overworked islands of Langerhans might be sufficiently put at rest by artificial supplies of insulin as to recover from their breakdown—after all, rest is nature's best restorative Occasionally what seems to be a genuine cure does result, but usually the rehabilitation of the islands is incomplete Frequently, however, enough restoration occurs to permit substantial decrease in the dosage of insulin

This account of diabetes is written under the implicit assumption that the mechanisms involved in the clinical variety are the same as those in the disorder produced by experimental removal of the pancreas This assumption is not necessarily true Like end results could be secured either from cutting down the production of insulin or by destroying it after it is produced Rabinowitch has published evidence that the latter may be an important factor in human diabetes In short, he has shown that the blood of the diabetic patient contains a substance that has a destructive effect on insulin This observation may account for the facts that when the pancreas of a patient dead of diabetes is studied sometimes little or no evidence of injury to the islands of Langerhans is found and that the gland yields considerable insulin

The account has been oversimplified, also, in omitting consideration of the liver There is evidence that no small part of the trouble is due to the inability of that organ to intervene normally in the transformation of sugar and fat to glycogen and vice versa The details of the relationship are still obscure

As a final clinical consideration, passing mention should be

made of a disorder at least superficially similar to true diabetes, in which the patient is nearly or completely refractory to insulin The blood sugar may rise to six or eight times the normal level The condition occurs sometimes in acute inflammation of the pancreas (*hemorrhagic pancreatis*) or as a manifestation of syphilis The disorder may possibly be due to excessive production of some sort of anti insulin, as was reported by Rabinowitch to occur in ordinary diabetes.

THE ACTION OF INSULIN—HYPERINSULINISM

From the foregoing statements the more outstanding effects of insulin can largely be deduced In the normal individual, it prevents the occurrence of the various abnormalities listed In the diabetic, it serves in a greater or less degree to reverse the processes to or toward normality

Unfortunately, however, if too enthusiastically supplied it overshoots the mark Not only is the blood sugar brought down to the proper level, but it continues to sink If the dose is sufficiently large, the patient first feels a peculiar sense of shaky weakness and then falls into convulsions or unconsciousness If a physician is summoned to deal with the condition, he sometimes finds himself in a quandary Is he dealing with that most ominous of events, a state of diabetic coma, or is it a manifestation of overdosage of insulin? In the one case, large doses of that very hormone are imperatively needed In the other, more insulin would probably kill the patient Prompt laboratory aid may be necessary to solve the dilemma Unfortunately, such aid is not always at hand In using insulin the proverbial "ounce of prevention" is of more than ordinary worth A small glass of orange juice or any other source of simple sugar suffices to ward off the danger If it is taken when the first shaky feeling is experienced, this quickly passes off and that is the last of that particular attack As a matter of practical common sense, insulin should never be given without provision for an immediate supply of sugar.

Is insulin ever "spontaneously" secreted in dangerous amounts? Apparently this problem was first investigated by Harris Recognizing that diabetes mellitus represents *hypo insulinism*, he reasoned that on general biological principles *hyperinsulinism* should also occur The first clinical case in which the condition was actually recognized was that of a physician in 1923 The symptoms upon which the diagnosis was made were "weakness, nervousness and irritability about an hour before dinner and supper, relieved by taking a soft drink" He also complained of the same symptoms and of wakefulness at night The blood sugar level was found to be 0 065 per cent as compared with the normal value, 0 80-0 120 His case was relatively mild It probably represented merely a slight exaggeration of the "all gone" feeling experienced by many people when they get unduly hungry

The next instance that was seen was more severe A laborer of fifty two complained of "excessive hunger, marked weak ness amounting at times to actual prostration, profuse perspira tion, trembling, anxiety and marked nervousness coming on three or four hours after meals" He got complete relief from an ordinary meal or from eating candy His fasting blood sugar, too, was 0 065 per cent With a slightly lower blood sugar—0 060 per cent—a boy of eighteen was found to have recurring attacks of convulsions and unconsciousness

Perhaps, in addition to simple oversecretion of insulin, some additional vulnerability factor—e g, pituitary deficiency—is involved in these mishaps This is suggested by an instance—also reported by Harris—of an obese man who had a blood sugar level as low as 0 045 per cent, but without any symptoms referable to that condition As we have had occasion to remark in numerous other connections, more research is needed

In a considerable number of cases such as those discussed, autopsy or surgical exploration has revealed tumor or simple hypertrophy of the islands of Langerhans In numerous in stances the condition has been relieved by removal of the ex cessive island tissue

While insulin is used in medical practice mostly for the treatment of diabetes, it is occasionally employed for other purposes One of these is to improve the general nutrition in *anorexia nervosa* and other conditions in which persistent underweight occurs Earlier belief was that the insulin served to increase hunger but, as mentioned in a previous chapter, the evidence that such is the case is not satisfactory Alternatively, it may serve to increase the appetite Whatever be the explanation, it is a fact that repeated injection of a few units of insulin a half hour before meals frequently does lead to a prompt and substantial gain of weight

Another use of the drug that has had considerable vogue in psychiatric circles is in the treatment of the psychosis *schizophrenia* (dementia praecox) It is given in sufficiently large doses to bring the patient to the verge of death in coma To safeguard against this disaster, reliance is placed in the fact that by injections of glucose the coma can be promptly terminated at will The patient is usually held in the unconscious state for two or three hours, then brought out of it with sugar According to the best statistics, the chances of recovery from the psychosis are improved at least twofold by the treatment, but in many cases the results are fleeting or nil How the improvement—when it does occur—is brought about is not known Possibly, as Cobb has suggested, it is by destroying the brain cells that are most at fault in the psychosis Another persuasive suggestion is that the patient is so forcefully brought back to reality as to overthrow his psychotic adaptation An alternative possibility is that the benefit comes from some unknown modification of the body metabolism

INFLUENCES OF OTHER GLANDS

In previous chapters the relationships to sugar metabolism of various hormones other than insulin was discussed Although the islands of Langerhans have been given the outstanding prominence, it is possible that the *hypophysis* may have quite

as fundamental significance As was first clearly shown by Houssay and Biasotti (1931), removal of the whole pituitary gland or of its anterior lobe alone markedly diminishes the severity of experimental pancreatic diabetes and renders the animal much more sensitive to insulin That the posterior lobe may also have a significant part in the carbohydrate scheme of things is suggested by Burn's discovery of the insulin antagonizing effect of pituitrin Another indication of a pituitary relationship is that properly treated diabetic children tend to average taller in stature than is normal for their age

A similar, and perhaps no less important, relationship is that of the *adrenal cortex* Adrenalectomy causes a lowering of the blood sugar and of the liver glycogen and these conditions can be restored to normal by cortical extract (Britton and Silvette) Long and Lukens have shown that adrenalectomy affects pancreatic diabetes much as does destruction of the pituitary The blood sugar is markedly lowered and supplementary injections of sugar may even be necessary to sustain life That destruction of the adrenal medulla alone has no effect on pancreatic diabetes has been shown by Rogoff and Ferrill, but single injections of adrenin do have a contrainsulin effect on sugar mobilization Conversely, some evidence can be found scattered through the literature of recent years that insulin in many respects serves as an antagonist of adrenin The one selectively stimulates the sympathetic system, the other may bear a like relationship to the parasympathetic system This has been shown, among other ways, by testing the reflex activity set up in the vagus nerves when the eyeball is pressed ("*oculo cardiac reflex*") Under the influence of insulin this reflex is reported to be augmented Similarly, after the injection of insulin the heart rate is slowed and arterial pressure decreased Cunningham and Lee showed that the decrease could be abolished by the administration of atropine and this fact, as physiologists well recognize, suggests that the phenomena are actually mediated by the vagus (parasympathetic) nerves Al

together, however, the evidence is somewhat inconsistent in tenor and inadequate in amount

The problem is complicated, moreover, by the fact demonstrated especially by Cannon and Britton that insulin tends to evoke a compensatory discharge of adrenin which precisely counteracts the effects previously noted It is only when the dosage of insulin is kept below the threshold of activating the adrenals that the uncomplicated manifestations can be seen The problem lends itself to more satisfactory research, as a matter of fact, in animals from which the adrenals are removed But since that operation is commonly fatal, only the relatively brief time in which the subjects survive in a state of approximately good health can be utilized for the study

Several facts indicate that the *thyroid* gland also has a significant relationship to carbohydrate metabolism Especially, destruction of this gland causes increased sensitivity to insulin That the influence is less fundamental than that of the pituitary and adrenals is indicated, however, by the observation that thyroidectomy does not materially influence the metabolic picture of diabetes

That the islands of Langerhans may have a significant relationship with the *ovaries* is indicated by the fact—noted in Joslin's clinic—that a considerable proportion of pregnant diabetic women show less than normal estrogen output in the urine and have difficulty carrying their offspring to birth In such cases injections of estrogen are significantly helpful (White) It has been reported, too, that removal of the ovaries of animals alters their sensitivity to insulin

CONTROL OF THE ISLANDS OF LANGERHANS

Whether the versatile anterior pituitary includes in its repertoire the control of insulin secretion is not known Destruction of that gland does not cause atrophy of the islands as it does that of the thyroid or adrenals Nevertheless, the pos-

sibility remains open that secretory efficiency might be impaired without actual morphological deterioration.

There is some evidence that insulin output is governed by the vagus nerve. For example, Gellhorn has shown that when the sympathetic adrenal mechanism is blocked, emotional excitement leads to a lowering of the blood sugar. When the adrenal medulla is intact, however, as was earlier shown by Cannon and Britton, a secondary discharge of adrenin occurs before the hypoglycemia progresses very far and thus restores the sugar level to or above normal. This reaction is one of the important homeostatic mechanisms emphasized by Cannon

The fact that pancreatic grafts without nervous connections function to hold the blood sugar levels within bounds indicates that the island cells are subject to control by the blood that circulates through them The effective humeral agent might be a hormone or might be the blood sugar itself. As Albritton first showed (1924), injections of glucose directly into the pancreatic artery can result in a lowering of the general blood sugar titer, hence we need, theoretically, to seek no further for an explanation Whether, however, the direct cell reaction to circulating carbohydrate is the sole, or even the most important, factor in regulating insulin discharge is a problem still in need of study.

THE BIOLOGY OF INSULIN

What is the fundamental significance of insulin in the physiologic scheme of things? Carbohydrate is our chief source of bodily energy. As men and animals conduct their daily lives the supply is irregularly replenished and the demand is likewise inconstant A device whereby the body cells are assured a constancy of carbohydrate offering is of obvious utility. This insulin affords. It helps to regulate the storage of carbohydrate when food is plentifully supplied and facilitates its use as the store is gradually given up to the blood But insulin does more. The human body as a machine is made up chiefly of protein as its structural material The body gets its energy from combus-

tion and protein is combustible Nature is faced with a problem somewhat similar to that which would be presented to an engineer if he had to construct an internal combustion engine of some such inflammable material as wood How can combustion be assured and the combustible machinery at the same time protected? In principle, the problem was solved by the development of an agency whereby the use of carbohydrate is so facilitated that the protein is spared

The foregoing account must be regarded as no more than an orienting sketch of the physiology of insulin Thousands of significant researches on this hormone have been published The data have become highly complex and many cannot yet be satisfactorily fitted into their final place in the completed picture

Several major problems remain only partially solved What is the exact structure of the insulin molecule? What are the physiological methods by which we are normally safeguarded from potentially dangerous oversecretion of insulin? What part does insulin play in the more fundamental aspects of metabolism? And perhaps the most important problem of all what regulates the regulator?

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XIV. SOME GENERAL ASPECTS OF ENDOCRINOLOGY

THE HORMONES AND ADAPTATION

BIOLOGY CENTERS in a paradox The organism, man or mouse, is made up largely of constituents that are most remarkable for their instability Sugar readily changes to alcohol Protein disintegrates so easily that a nearly fresh egg is a culinary abomination Fat turns rancid It is of such stuffs that the living substance, protoplasm, is made This labile mass is exposed on all sides, without and within, to forces that threaten its disintegration Out of this composite instability emerges the stable individual The "steady state"—indeed, the very existence of the organism—is rendered possible only by a highly developed ability to respond appropriately to the multitude of disturbing influences to which it is constantly exposed The complex of protective mechanisms that are employed to this end are subsumed in the term *adaptation* They and their operations are discussed at length in Cannon's book *The Wisdom of the Body*

The higher organism is made up of a multitude of tissue cells each having its own physiological autonomy The cells correspond to the individual citizens in a social system Groups of cells, in turn, form organs in which the different varieties co-operate to a specialized end as do the citizens, for example, in a mill village Finally, the various organs are integrated into a unity that might be likened to a commonwealth An important aspect of adaptation is the control of the individual

cells and organs to the end that all shall function co-operatively for the welfare of the individual as a whole

Of the various controlling mechanisms, that most widely known is the nervous system This may be likened to a tele phone system of a great city Messages are constantly going from the various parts of the organism to co-ordinating and distributing centers and thence transmitted to the various end stations In large measure, the messages are individual In this book we are dealing with another controlling system, in which the messages are not thus individually distributed but are broadcast to the organism as a whole Such selectivity as there is in the reception of the messages is closely analogous with that of a radio broadcast The various receiving instruments themselves determine the matter By and large, hormone broadcasts are utilized to bring about responses in which the body as a whole, or major portions of it, respond The utility of this system in the conservation of nervous energy was previ ously discussed

Another general characteristic of the hormones is that they mostly influence functions that are in greater or less degree periodic Even a growth curve is a rising line with superim posed fluctuations, the major waves being at the prenatal and early puberal epochs Corresponding with the rhythms of the body are the hormone tides The reproductive functions and the digestive activities may serve to illustrate this principle Perhaps the most striking of all the periodic functions is sleep Whether this, too, is to any significant degree under hormone control, direct or indirect, has not been satisfactorily deter mined The occasional occurrence of pathological somnolence in Fröhlich's disease to some extent suggests that as a possi bility

In the discussion of the parathyroid glands a third principle was suggested Although most of the chemical constituents of the body are labile, i e, they react with other substances rather readily, in a few instances sluggish compounds are used, com pounds that presumably could not be utilized at all without

special provision to facilitate their reactivity For example, in the regulation of lime metabolism the molecules, calcium phosphate and calcium carbonate, are now withdrawn from, and now added to, the bony tissue So inert are these substances that one of them, the carbonate, is used as an ingredient in the plaster of the walls of our homes There its very inertness is a chief virtue Year after year it remains unchanged while the wood under it slowly disintegrates As agents to facilitate sluggish reactions, the hormones would fall with the enzymes in the general class of substances known as *catalysts* The particularity suggested for the parathyroid hormone, however, is only relative Thyroxine and adrenin also act like catalysts in the oxidative processes and catalysis may be the *modus operandi* of hormones in general Just how the catalytic influences are actually mediated, whether the hormones enter into combination with the tissue substances or whether they act by altering the physico-chemical status of the tissue cells and their membranes, is mostly not known

THE HORMONES AND THE NERVOUS SYSTEM

We have referred to nervous and to hormone control as though they were separate and independent processes As a matter of fact, no little part of the effectiveness of the two methods results from the fact that the hormones frequently influence the nervous system and the nervous system influences the endocrine glands Adrenin, it will be recalled, exerts its effect almost, if not exclusively, through the (peripheral) sympathetic nervous system Any structure that does not have sympathetic innervation does not respond to that hormone Secretin, on the other hand, evokes an outpouring of pancreatic juice apparently quite as well from a denervated as from a normal gland Insulin probably acts both through the nervous system and directly upon the various tissues in which carbohydrate is dealt with

Similarly, the action of the nervous system on the endocrine

organs may be illustrated Here, again, the adrenal will serve The discharge of adrenin normally takes place, so far as we know, only when impulses are relayed to that gland over its sympathetic nerve fibers (except as asphyxia may have a direct stimulating effect) If the nerves to the gland are cut, a variety of influences which customarily call out the adrenal response are no longer effective to that end The corpus luteum, at the other extreme, appears to be entirely independent of nervous influences, though it is quite responsive to a hormone from the anterior lobe of the pituitary The thyroid seems to fall in an intermediate position It can be transplanted from its normal location to any suitable place in the body and there it will continue to supply thyroxine in sufficient amount to maintain normal health The graft receives no nerve impulses On the other hand, there is some direct evidence and considerable presumptive evidence that the thyroid under other circumstances does respond to nervous influences Many instances have been reported in which nervous tension has seemed to be the chief factor in lighting up exophthalmic goiter (hyperthyroidism) in man It must be confessed, however, that despite many efforts to determine the matter we are still mostly at sea regarding the nervous control of the thyroid gland

INTERRELATIONSHIPS AMONG THE ENDOCRINE GLANDS

Not only is the story complicated by the relationship of the nervous system to the endocrine organs and of the endocrine organs to the nervous system, but still further by the relationships of the various endocrine organs with each other So intimate and common are these interactions that it is doubtful if such a thing as a uniglandular disorder can actually exist

The evidence is rather respectable that removal of the thyroid gland causes enlargement of the pituitary and, presumptively, increase of its secretions Destruction of the pituitary, in turn, results in depression of the activity of the thyroid It is for this reason that tadpoles cannot change into frogs after

that operation In further illustration, Sharpey-Schäfer cites this train of events The thyroid by its internal secretion stimulates the adrenal medulla, the increase of adrenin thereby caused provokes the liver and other cells to discharge their glycogen into the blood as glucose, and the elevation of the blood sugar thus produced stimulates the islands of Langerhans to secrete insulin, this in its turn facilitates carbohydrate metabolism and affects the nutrition and activity of most of the tissues and organs of the body If the secretion of the anterior lobe of the pituitary fails, the functions of the gonads are depressed Removal of the gonads, in turn, causes a change both in the structure of the anterior pituitary and in its hormone content

In some instances hormones seem to interact to promote a given end For example, thyroxine and adrenin cause an increase in the rate of oxygen consumption Estrogen and progestin apparently co-operate to stimulate the walls of the uterus but progestin in other respects counteracts the estrogen either in its production or in its influence Thus, while the ovary contains active corpus luteum tissue, both ovulation and estrus are kept in abeyance

A detailed discussion of other interrelationships, proved or suspected, would carry us too far afield Several writers have published intricate charts purporting to set them forth in all their complexities Few, if any, of the more elaborate diagrams are justified by the actual evidence we now possess Nevertheless, the interrelationships are important and serve to set many a puzzling problem to the diagnostician

The fact that the body is under multiple hormone control carries mathematical implications that are frequently given less than their due consideration Since each of the glands can produce its secretion or secretions in subnormal, normal, or supranormal amounts, three bodily functional patterns can be set up through the agency of each hormone acting independently When a second hormone enters the picture, each of its three levels of activity can be combined with the three levels in the

other, giving rise to nine combinations Three hormones give twenty seven permutations, and so on Thus, with the addition of each gland, the complexities increase *geometrically* The permutation formula is three to the n'th power, "n" being the number of hormones involved When "n" increases to sixteen —and nature probably operates with at least that many hor mones—the permutations extend to more than forty millions Each of these would theoretically represent a different bodily condition, only one being that due to normal level of all the sixteen How many millions of glandular disorders that are theoretically possible actually exist is entirely unknown, but presumably there are many more than have yet been recog nized clinically As a matter of fact, however, attempts such as this to apply cause and-effect logic to such intricate systems are rather inept The different conditions actually merge into each other What we are confronted with is a complex of shift ing equilibria in which causes and effects are inextricably mingled

FACTORS IN HORMONE RESPONSE

In a large part of the endocrine literature the assumption is tacitly made that the only important variables in hormone equations are alterations in secretion levels in the different glands But quite as important, perhaps, are variations in the ability of the body to react to a given hormone If, for example, the reaction threshold to thyroxine were high, the individual might in effect suffer from thyroid deficiency even though his glands were secreting at a normal rate For some unexplained reason, many subjects of the schizophrenic psychosis actually show such sluggishness of reaction to this hormone, often fail ing to respond significantly to several times the dosage which is effective in normal people Little is yet known as to the fac tors which influence tissue reactivity to the hormones But, as previously noted, fragmentary evidence indicates that some of these are the acid alkaline balance of the tissues, the tempera ture of the body or of the environment, the age and sex of the

subject, the nutritional condition of the tissues, and the available supply of vitamins The inorganic salt content of the cells also seems to be of importance Some factors which probably influence both the tissue response and the level of hormone production in the various glands are season, environmental temperature, diet, age, sex, levels of activity of related glands, and phases of the sex cycle

DUALITY OF THE GLANDS

A striking feature of several of the endocrine organs is their structural duality The pituitary body consists of two distinct parts, the anterior lobe and the posterior lobe with its adjacent epithelial tissue Extracts of the two portions have very different effects, the one from the other In many animals the thyroid and parathyroid glands are closely associated anatomically The adrenals in the higher animals consist of two parts, the cortex and the medulla that it encloses Here, again, extracts of the parts have quite different properties The corpus luteum is enclosed in the ovary and its characteristic hormone is different from the estrogens

But in some animals the parathyroid glands are quite separate from the thyroid and seem to function equally as well as those that are incorporated with it Also in many of the lower forms—for example, fishes—the two parts of the adrenal gland are anatomically entirely distinct In the whale the anterior and posterior lobes of the hypophysis are structurally independent Have the afore mentioned anatomical associations, then, a physiological meaning or are they simply architectural accidents? The problem is left for those who may like to speculate upon it

EVOLUTION OF HORMONE CONTROL

The biologic philosopher may also enjoy setting his teeth in this problem in the evolution of the higher animals have the hormones been developed to govern the reactions and growth

changes to which they give rise or have these latter been secondarily evolved in relation to the hormones? Which is horse and which is cart?

A few suggestive facts may be cited Chemical control is found at the very bottom of the scale of animal life It increases in complexity as the body becomes more complex For instance, carbon dioxide is produced in the most primitive forms When, relatively late in the evolutionary course of events, a complex respiratory system came into being, its control was relegated largely to carbon dioxide, which had been a common metabolite from the beginning It is not unlikely that the development of hormone control has taken a similar course The thyroid gland, the anterior lobe of the pituitary, and the islands of Langerhans arise in the embryo from the digestive system The best guess is that originally they were glands that produced digestive juices As such, each no doubt had its own peculiar chemistry and formed its own sort of end products Perhaps the body has merely developed adaptive reactions to these products and the glands have more and more specialized in forming them and finally given up entirely their original office of secreting digestive juices

The supposition that the bodily reactions are secondary developments is borne out by the fact that some animals produce hormones that have a marked influence on organs that the animals themselves do not possess For example, extract of the posterior lobe of the hypophysis of a fish or a bird stimulates the uterus of a cat, yet neither the fish nor the bird has a uterus of its own

HORMONES AND RACIAL CHARACTERISTICS

In the first chapter, brief attention was given to the part that hormones may have played in the development of racial types The writings of Keith and of Stockard were mentioned As is well known, the different races of mankind vary rather markedly in various respects, e g, stature The tall northern Eu

ropean stands in striking contrast with the African pigmy. We are well aware that the growth hormone of the anterior pituitary is capable of exercising a profound influence upon the length of the body and of the limbs of the individual subject. Conversely, deficiency of this hormone results in individual dwarfism. The supposition is by no means extravagant that the Nordic is now tall because of the gradual emergence of anterior lobe dominance in his ancestral past. Another possible factor in the regulation of height is the action of the gonad hormones. Castration tends to cause delay in the closure of the growth zones of the long bones and persistence of skeletal growth well past the normal age of puberty. That the fervent, early-maturing short races may have derived their bodily and mental characteristics, in part at least, from gradually developing preponderance of the gonadal hormones is possible, if not probable. Conversely, the more phlegmatic, late maturing tall races may have derived some of their characteristics from relative inefficiency in the secretion of these hormones

In addition to variations in growth, the endocrine organs are capable of bringing about changes of configuration. The heavy features, the protruding jaw with widely spaced teeth, the beetling brows, and the gorillalike proportions of the acromegalic afford convincing evidence of the potency of the anterior pituitary growth hormone. Similarly, the configuration of the child suffering from marked thyroid deficiency is characteristic. The growth of the skeleton in general is arrested, but changes in the structure of the head are particularly prominent The base of the skull, especially, fails to develop, with the result that the root of the nose seems to be flattened and retracted between the eyes On the other hand, the upper forehead projects These are the features, as Keith points out, that give the Mongolian face its peculiar characteristics The face of the Negro shows, in less degree, the same features. Indeed, in one aberrant branch of this race, the Bushmen, the suggestion of thyroid deficiency is even more marked than among Mongols The theory that the thyroid is a determining factor

in the respects listed is attractive, but considerable ingenuity is required to make it fit the facts For example, the most characteristic result of thyroid deficiency is a depressed basal metabolic rate Mongols show this only to slight degree, if at all They are also fecund, as hypothyroid subjects are not

Differences in skin and hair of various races are striking Adrenal deficiency sufficiently pronounced to cause Addison's disease leads to a marked darkening of the skin Keith is accordingly inclined to ascribe a significant role to relative adrenal-cortex deficiency in the production of the skin coloration in the darker races But adrenal deficiency is especially characterized by bodily weakness, and some of the Negro tribes are notable for their strength An oversupply of the cortical hormone is one cause of precocious puberty, hence, deficiency of this hormone would presumably result in delayed puberty Such is not characteristic of Negroes, the dark races tend to mature earlier than the light The evidence is thus ambiguous

On the whole, the theory that the pattern of evolution has been set by the bormones is not lacking in plausibility It is, however, by no means adequately supported by specific factual evidence Whether the anterior pituitary of an adolescent Swede actually produces relatively more growth hormone than does that of a pigmy is not known Perhaps the nearest approach we have to cogent evidence is the fact reported by Riddle that it is possible by selective breeding to produce races of doves characterized by large or small thyroid glands It is thus shown that nature could have made use of such a working plan whether she actually did so or not

The theory under discussion need not be restricted either to stature or to gross configuration The metabolic trends of the individual might likewise be determined by his endocrine inheritance Pende, indeed, has written at length on this topic He lays a great deal of stress on "endocrinopathic constitution" as determining bodily efficiency or liability to disease As a case in point, investigators are now working on the possibility that susceptibility to infantile paralysis may be determined by

the endocrine constitution. The conception is capable of wide extension.

Finally, the mental and emotional trends of the individual may also be determined in large measure by his hormones, and these trends may be hereditary. Of late years much has been written on this topic. But before psychology, sociology, and criminology can be convincingly rewritten as merely special aspects of endocrinology, many more facts than are now available will have to be collected and integrated.

ENDOCRINE DIAGNOSIS

"Time was in the memory of living men when pathology—the graveyard pathology of the earlier day—was a matter of small interest and less significance to the practitioner of everyday medicine." It was not until the older pathology was blended with physiology that it came to be meaningful to the doctor in his everyday work. But the physiology of the past was not the physiology of today It is only in our time that the permeating influence of the hormones in the life processes of every cell has become apparent. Physiology without the hormones is not physiology at all. Since pathology is but physiology out of balance, an extension of the generalization is warranted—pathology without the hormones is likewise incomplete pathology. Since the hormones determine health, they must likewise play an important role in disease processes generally. Hence, to a greater extent than is commonly recognized, endocrine diagnosis is a matter of importance to every physician. Not only in the endocrine disorders proper, but also in "non endocrine" diseases, the functional status of the various glands is a matter of moment.

What would be ideal for accurate diagnosis would be methods of determining the precise level of secretory activity in each of the living glands. Perhaps someday analysis of the blood for its content of the various hormones may be possible. That would solve the problem of diagnosis at a stroke Further-

more, it would permit the revision of the diagnosis as frequently as necessary to keep pace with changes in the patient So far only a beginning of such blood assaying has been made —as in the case of the sex hormones

When the theory of antihormones (discussed below) was proposed, hope was aroused that the problem of direct diagnosis might be well on the way to solution Thus, to determine the thyroxine content of a given sample of blood, it could be titrated against a known solution of antithyroid agent somewhat as a chemist titrates an acid against an alkali In that analogy, the "indicator" would presumably be the living test animal into which the solutions would be injected Ultimately, however, physical or chemical indicators might be evolved But all this is for the future

A detailed discussion of all the present-day resources of the diagnostician would go beyond the proper scope of this book The working endocrinologist relies primarily upon the methods of good practitioners in any field of medicine He first makes searching inquiries regarding the family background and the personal history of the patient When and how his malady first became apparent may tell much as to what is fundamentally wrong Detailed knowledge of the sequence of developmental changes is especially enlightening

The history is then supplemented by a complete physical examination to determine the presence and degree of deviations from normality In this undertaking nice judgment as well as familiarity with body types and normal variations is needed Especially significant are skeletal proportions, nutrition, and hair and fat distribution

A few endocrine disorders are so plainly written upon the victims that he who runs may read A typical case of childhood myxedema can be recognized at a glance The diagnosis of diabetes mellitus in its typical form is almost as easy But for the recognition of other disorders, for example, the lesser degrees of thyroid or pituitary deficiency, intricate metabolic studies may be required A variety of laboratory procedures

can be brought to bear The basal metabolic rate is determined, the blood and urine are analyzed for a variety of constituents The information thus derived may solve the problem If not, it then becomes one for the specialist

ENDOCRINE THERAPY

Successful treatment of glandular disorders rests upon two necessary conditions, namely, recognition of the kind and degree of abnormality that is to be treated and the availability of potent preparations to be administered In addition, there remains to be considered the endocrine treatment of non glandular disorders

Some of the difficulties of diagnosis have been discussed in the preceding section In some instances, primary glandular defects are fairly easy of recognition, but others require elaborate procedures for their identification, and for still others, the existence of which is theoretically probable, adequate diagnostic procedures are still unknown

Perhaps the greatest difficulty that confronts the endocrine practitioner arises from the fact that the various glands stand in intimate relationships with each other so that a defect in one is secondarily reflected in the functional behavior of others The conventional procedure for meeting this difficulty is to attempt to determine the primary disorder and to treat it in the hope that the secondary manifestations will thereby be corrected In other words, the endeavor is to shift the displaced glandular equilibrium from an abnormal back to a normal point Often this method is successful For example, in thyroid deficiency, when it is recognized sufficiently early, treatment may be completely successful in restoring normality throughout the body Success in this, the uniglandular type of treatment, however, may fall well short of completeness for either one of two reasons A potent preparation of the gland immediately at fault may not be available or secondary changes may have progressed to the irreversible point In either contin

gency, better results may be obtained when the treatment is addressed to the secondary defects exclusively or to these in addition to the primary defect

The interglandular relationships give rise to another sort of handicap when replacement therapy is attempted For example, suppose that one undertakes to correct a sluggish uterine condition by the use of estrogen While that organ is being stimulated the ovaries are likely to be depressed, so that what is gained in one direction is lost in the other Furthermore, the primary sex hormones apparently all have a secondary depressing effect upon the anterior pituitary, again with compensating gain and loss Theoretically—and perhaps actually—the secondary depression in the pituitary can be more or less adequately treated by the adjunctive use of thyroid material This, in turn, presumably would depress the thyroid, but that consideration would not be important because thyroid material is inexpensive and enough additional can readily be given to make up for the induced thyroxine deficit This consideration may account for the fact, which has often been empirically noted, that the addition of thyroid improves the therapeutic action of several other hormone preparations

Another difficulty arises in the use of the estrogens Nature uses them in cyclic sequence with progesterone and hence they should not be given out of phase because of the danger of disrupting the cycles In addition to the primary disorganization thus set up, a secondary disruption is reflected in the anterior pituitary, which also secretes the corresponding stimulating gonadotropins in phase The physician attempts to meet this difficulty by giving estrogen and progesterone alternately in imitation of nature's order When the patient's menstrual periods can be utilized for orientation, the proper sequence can often be fairly well determined, but in cases of irregularity or suppression of menstruation this aid is not available Some success, however, can be anticipated by arbitrarily setting up an alternating periodicity in the medication in the hope that nature will fall into step

Such procedures are at best, however, but a poor imitation of nature's use of the hormones Since the relative amounts of both estrogen and progesterone vary with each day of the cycle, the artificial dosage should likewise be changed from day to day, but, practically, this can scarcely be done Each patient is more or less a law unto herself as to how much hormone is needed on any given day and the regimen would be impracticably complex

Still another difficulty in imitating nature's procedures is that the hormone output varies adaptively in accordance with immediate needs, whereas hormone injections necessarily set up series of feasts and famines In case of preparations that can be taken by mouth, however, the lag in absorption can be utilized to secure fairly smooth intake In some instances, constancy of input can also be attained by implanting pellets of the material beneath the skin But this resource fails, of course, to imitate adaptive changes in the natural secretion rate

In addition to their use as agents for replacement thereapy, the hormones can sometimes be legitimately used as diagnostic agents This use is based upon a fundamental physiological law that the response to a stimulus depends largely upon the amount of that stimulus which is already acting A classic illustration of the principle is that when a ten pound weight is resting upon the hand the addition of another ounce makes little difference, but when the initial weight is only one ounce the second ounce is relatively much more noticeable While the principle (Weber Fechner law) was originally worked out in terms of sensory perception, it seems to be valid also for metabolic stimulation For instance, if the thyroid gland of the individual is secreting an adequate amount of thyroxine the daily administration of an additional grain of thyroid substance has little or no perceptible effect If, however, the tissues are starving for the hormone they seize avidly upon any that is offered and may seriously overreact to it To employ this principle for a therapeutic test of glandular deficiency, a standard dosage of the given hormone preparation is administered Any marked

reaction to it is strong presumptive evidence of a corresponding deficit This principle obviously lends itself to abuse in that it can be used as an excuse for slovenly diagnostic work Thus, in case of doubt, a "shot gun mixture" can be administered in the hope that nature will pick out what is needed and ignore the rest Such a method is objectionable on the score that it entails the purchase of useless and often expensive material, and that it may, after a time, subtly upset the normal endocrine balance of the body

Theoretically, hormone preparations might be valuable in the treatment of a variety of nonglandular disorders by virtue of their drug effects Since thyroxine stimulates all the body cells, it might be regarded as a very excellent general tonic. As previously mentioned, however, it has not been very successful for this purpose The hormones that have proved to be the most valuable merely as drugs are adrenin and pituitrin Adrenin, as mentioned in an earlier chapter, is frequently used for the relief of asthma and as a rapidly acting heart stimulant In some sorts of collapse it may be injected directly into the heart itself and for this purpose is often lifesaving The fact that its influence is notably short lasting limits its value Attempts have been made to incorporate adrenin in some vehicle from which it will be only slowly absorbed, but its field of usefulness has not, as a practical matter of fact, been greatly extended by this means The chief use of pituitrin as a drug is, as previously mentioned, to overcome uterine sluggishness and thus hasten the birth processes It is a fairly effective agent also for the stimulation of the bladder wall or intestines, especially in postoperative conditions The uses of insulin for the improvement of nutrition and in the treatment of the schizophrenic psychosis were also mentioned in an earlier chapter

The potency and reliability of endocrine preparations vary widely At the head of the list stand thyroxine or desiccated thyroid substance, adrenin, insulin, and pituitrin When the indications for the use of any of these materials are present, they can be given in high confidence of satisfactory results

Cortin, too, is effective but potency is somewhat difficult to maintain Several excellent sex hormone preparations are also available, and when their use is based upon adequate diagnosis the results are often satisfactory Several synthetic hormones or hormonelike materials are available, and since the composition of these is accurately known reactions to them are correspondingly predictable On the whole, the least reliable of the hormone preparations are those which are themselves proteins Because of the effect of the digestive juices upon them, they have to be given hypodermatically They are likely to disintegrate and lose their potency with the passage of time and are more or less likely to cause the formation of interfering antisubstances Being highly complex, the protein hormones will be difficult, if not impossible, to make artificially

The foregoing discussion has to do mostly with the treatment of hormone deficits The problems presented by overactivity are in principle much simpler Theoretically, all that is needed is to destroy enough of the offending gland tissue to restore normality in the secretion level The most direct means to this end is surgical excision When, however, the pituitary is the gland at fault, the surgery is complicated and dangerous Another difficulty that is both theoretical and practical is to determine how much of the glandular tissue should be removed Not to put too fine a point upon the matter, reliance has to be placed upon the educated guessing of the surgeon Destructive chemicals might be injected into the glands, but the difficulty of controlling their penetration and sphere of action is so great that relatively little use of them has been possible Finally, in some cases the application of destructive doses of X ray or radium can be used

Many brilliant successes have rewarded the efforts of the endocrine therapeutists but also, under present-day limitations, disappointments and failures are likewise often met With each passing year, however, as better preparations become available and as more skill in their use accrues, results improve While no therapeutic millennium is likely ever to

arise out of endocrinology, increasingly important additions to the physician's armamentarium are to be hoped for Possibly, when more shall have been learned about the control of the various endocrine glands, methods may be found of increasing or decreasing their levels of secretory activity by the use of appropriate drugs, or even by the selection of diets That is a development, however, for the future

ANTIHORMONES

Previous mention was made of the possible importance of antihormones As is well known, the injection of foreign protein substances into the body commonly leads to the production of protective "antibodies" It is through an aberration of this phenomenon that many kinds of allergy arise The body shows surprisingly delicate discrimination as to what is "foreign" and what is "native" protein The injection of tissue extract from an animal of any species evokes the reaction from one of any other species even though all precautions are taken to avoid chemical changes in the proteins themselves In view of the fact that several of the hormones are proteins, it might be anticipated that cross injections of these from one species to another would lead to production also of specific hormone antibodies The only theoretical escape from that assumption would be to postulate that the true hormones are identical molecules irrespective of the body composition of the species in which they originate Such an assumption is intrinsically improbable

According to Collip, the idea of the production of a specific inhibitory substance which circulates in the blood stream and is able to neutralize the effects of a hormone was probably first expressed by Mobius in 1906 He reported that the blood of thyroidectomized sheep neutralizes the reaction of thyroid hormone The first attempt explicitly to obtain a hormone neutralizing substance by injecting an endocrine preparation was probably made by Blum He coined the name "catechin" to

designate such inhibitory substances (1933) The term "anti hormone" was used by Wiese as early as 1928 Further discussion of the earlier studies and of the attempts to adapt them to clinical purposes would go beyond the scope of this book

The first clear demonstration of the appearance of hormone antagonists in the blood as a result of pretreatment by hormone preparations was published by Collip and his associates in 1934 Antihormones for the thyrotropic and the gonadotropic factors were announced It was concluded, however, that the antihormones are probably not comparable to antibodies in the usual sense of that term

During the intervening years many studies have been made, some of which have supported and some of which have failed to support the primary conception Expert opinion is still divided as to whether true antihormones actually exist Many of the results that have been secured could be explained as due to the ordinary immunological antibody reactions Alternatively, in some cases, it is possible that the production of antagonistic hormones of known varieties has been stimulated The outstanding undisputed fact is that, whatever the mechanism or mechanisms may be which account for the fact, it is true that prolonged use of various hormone preparations leads finally to loss of reactivity to them For example, injections of pituitary thyrotropic preparations bring about early stimulation of the thyroid gland with the production of something closely similar to exophthalmic goiter Within a short time, however, the reaction wanes and the pretreatment condition is resumed despite the continuation of the injections Similarly, in clinical practice, parathyroid extracts after a time lose their efficacy

From a rather exhaustive survey of the literature, Collip (1940) set forth the following as the most important facts that were then definitely established The blood of animals persistently treated with gonadotropic or thyrotropic preparations acquires the ability to neutralize the action of such preparations in other animals The antibodies are specific in the sense that one which antagonizes the action of a given hormone

has no similar property as regards another For example, anti gonadotropic hormone does not antagonize the action of thyrotropic and vice versa The blood of an animal rendered immune to a given type of gonadotropic preparation, though very active in neutralizing the action of this preparation, may be relatively inactive with regard to other gonadotropic extracts Similar examples of extract specificity have been found in case of the antithyrotropic hormone Neither the presence of the target organ of a given hormone nor of the organ in which it originates is essential for antihormone formation For example, antithyrotropic hormone can be produced in the body of an animal having neither thyroid nor anterior pituitary gland. There is little or no evidence that chemically pure hormone preparations, such as estrogens or adrenalin, form antihormones in the true sense of the word, though the sensitivity of the organism to such preparations may decrease after prolonged treatment.

To whatever extent true antihormone production occurs, the mechanism is probably important as a regulatory device to protect the body from harmful effects when conditions arise that lead to the production of hormones in excessive amounts The very fact, however, that such conditions as gigantism or exophthalmic goiter can persist over a period of years indicates that antihormone production is by no means an unfailing resource

OBESITY

In previous chapters the occurrence of obesity as a feature in various glandular disorders has been noted The outstanding evidences may now be brought together in summary form Some clinical endocrinologists assume the existence of several definitive types of obesity of endocrine origin, and many diagnoses of endocrine disorders are made in whole or in part in the light of this assumption Other endocrinologists hold, however, that there is little specificity in the relationships and, indeed, that endocrine factors play a relatively small role in the production of obesity of any type.

As emphasized in an earlier chapter, the ultimate cause of any obesity is the consumption of more food than is utilized Entirely consonant with this fact, however, is the possibility that glandular factors may influence both hunger or appetite and efficiency in the use of food Thus, one person may habitually remain thin in a sedentary occupation while consuming regularly twice as much food as some other person whose waist line gradually and discouragingly increases, despite exercises Perhaps the most impressive item of evidence of hormone intervention in the nutritional situation is the fact that the stimulating value of food—its *specific dynamic action*—is decreased in conditions of thyroid deficiency A similar claim is made for the anterior pituitary, but the evidence is less convincing

Attention has been called to the operation of the endocrine factors which bring about a reduction in the blood sugar level When this reduction arises from unusually rapid tissue storage of the products of digestion, the resulting blood depletion may set up abnormal hunger This, in turn, may lead to undue food consumption with resulting *hypoglycemic obesity* Theoretically, either one or all of several glands might be involved in this condition, especially the anterior pituitary, adrenal, and possibly the thyroid gland or the islands of Langerhans might be at fault

Hypothyroid obesity, although, according to Sevringhaus, uncommon, is generally recognized as a genuine clinical entity It may be seen not only in cretinism and myxedema, but in other cases in which the thyroid deficiency is objectively less obvious The fat is rather generally distributed but seems to have some special predilection for the neck and shoulders The diagnostic problem in differentiating thyroid obesity from other types is the same as that of diagnosing thyroid deficiency in any guise The condition yields satisfactorily to skillful thyroid treatment supplemented as needed by measures of dietary management

Pituitary obesity has been the subject of much clinical debate Perhaps the most common type of this disorder is the

Frohlich syndrome or adiposogenital dystrophy In the foreground of the picture stands failure of development and function of the gonads Behind this failure often lies, apparently, deficiency of anterior pituitary secretion The difficulty in generalizing arises from the fact that marked degrees of anterior pituitary deficiency may exist—as in dwarfism—without the appearance of obesity—and, indeed, some sorts of pituitary inadequacy, e g, that of Simmonds' disease, are characterized by leanness Frequently, women have much trouble keeping down their weight after *pregnancy*—a fact which suggests lasting repercussion of that state in the pituitary function However, precise evidence for the assumed pituitary abnormality as a factor is often lacking Often in pituitary obesity the forearms, hands, and fingers remain unaffected as do also the lower legs and feet Some endocrinologists regard the presence of delicate extremities in fat subjects as conclusive evidence of pituitary involvement In the treatment of pituitary obesity, gonadotropic extracts are sometimes effective and sometimes not Thyroid is often given, but is not nearly as effective as in the hypothyroid type

A considerable part of the difficulty in both diagnosis and treatment of this group of disorders arises from the fact that the primary defect may lie not in the glands as such, but in the hypothalamic controlling centers When the latter is the essential condition, the term *hypothalamic* obesity is applicable The disease *encephalitis lethargica* is particularly likely to leave permanent effects in the hypothalamic area and thus to be followed by overweight

Other conditions in which obesity occurs generally or frequently are the Lawrence Biedl syndrome, pituitary basophilism, and possibly hyperplasia of the adrenal cortex The frequent association of this condition with primary gonadal deficiency, as after castration or spaying, is also well known In the latter type, the fat tends to accumulate especially in the hip and breast regions In the Cushing syndrome, the obesity is confined to the trunk, the arms and legs being spared

A tendency to fatness runs in certain families, hence it is known as the *familial* type The diagnosis obviously begs the question of immediate causation, any of the mechanisms above discussed might account for it in case they, in turn, were transmitted characteristics

Generally speaking, when the physician can succeed in tracing obesity to an explicit glandular disorder treatment addressed to this cause is rather successful Lacking such reliable incrimination, however, hit or miss endocrine treatment is likely to be more expensive than satisfactory In such cases, skillfully managed dieting is the chief reliance Though thyroid used with discretion under medical guidance may be a helpful adjunct, in unsophisticated hands it is a dangerous resource It is often the presence of thyroid substance in ready made "fat cures" that renders them unsafe for lay consumption

Whatever reliance may be placed in gland therapy, the control of food intake is important There is no royal road to slimness—endocrine or otherwise Adjustment of diet, beginning early in the course of the disorder, is much better than vigorous reduction treatments later A first requisite in either case is to see that a good balance of the essential food elements and vitamins is insured Devotion to dietetic tricks and fads is especially likely to result in failure in this regard There is much opportunity for skill in prescribing diets, in adapting them to the personal likes and dislikes of the recipients while still retaining good balance Perhaps the most difficult matter to control is a propensity for taking "just a bite or two" of this or that between meals This indulgence must be rigorously interdicted Alcoholic beverages and sweet drinks, too, can easily vitiate a reducing regimen In some patients restriction of fluid and salt intake as well as that of calories is necessary

ENDOCRINE FACTORS IN PERSONALITY

Many elements enter into the make up of the personality Some of these are hereditary and some acquired The human

infant brings into the world with him elaborate equipment for living In many respects the equipment is fixed, but in many others considerable leeway exists for the modification of the constitutional characteristics Objectively, personality must be studied in terms of behavior, though many of our most cogent data are items of subjective experience However, introspective psychology is difficult to deal with scientifically, hence will not be brought into this discussion

A commonly overemphasized factor in personality is the *intellect*—the operation of the higher mental faculties This is actually a recent acquisition in the course of human evolution From the point of view of the biologist, the intelligence is mostly a device to secure for the individual maximal gratification of his instincts In everyday use its chief function is to rationalize the things that we do because we instinctively want to do them This fact explains why appeals to the intelligence by the savant are so much less effective than appeals to the "lower motives" by the demagogue However important the intelligence may be as a factor in personality, it is determined in part by endocrine factors. The clearest indication of this relationship is in the mental retardation seen in higher grades of thyroid deficiency

More important in the determination of the personality are the *instincts* and the *emotions* The instincts may be roughly defined as the behavior trends that are determined by the constitutional make up The emotions represent the way the instincts in operation feel to the individual who has them It is the instinctual drives that the psychoanalyst has mostly in mind in his use of the term "id forces" The instinctual trends are determined in considerable measure by the hormones

This relationship is most clearly evident in the sex sphere In the lower animals it is unmistakable As pointed out in previous chapters, both the existence and the quality of *sex behavior* are so determined In the human species the operation of the gonad hormones is less sharply defined, though the principles are fundamentally the same The human eunuch is re

ported as lacking in initiative and stamina, as "lone wolf," quiet, retiring, shut in, and work-shy The picture, however, varies a great deal in its ultimate development and some individuals completely or largely devoid of primary sex hormones seem to be not greatly handicapped by the deficit The mentality, as such, is apparently little affected, and indeed the mental attainments may be improved by freedom from the diversions and distractions incident to the possession of gonadal hormones It is the personality as distinct from body or mind, as such, in which the defect is chiefly apparent

The effects of gonad deficit are most evident when they arise in the *prepuberal* years The boy deprived of his primary sex glands remains throughout life emotionally immature Into his ear the soft voice of love does not enter Romance with all the connotations of that term is not for him In the girl, as far as the rather scanty evidence goes to show, primary lack of ovarian hormones has a similar influence Neither the bodily nor the psychological differentiation normal to puberty can take place In the adult years, as in childhood, no more than platonic interest in the opposite sex is shown Courtship offers no charm and there is neither inclination nor ability successfully to mate

When the gonadal deficits arise in *adulthood* the effects are much less clear Rowe's unflattering characterization of the female hypogonad temperament was previously quoted Acute ovarian deficiency is unquestionably associated with a trying hormonal imbalance After a time, however, inner adjustment is attained and customary placidity of demeanor largely restored Actually, how much of the "sour old maid" temperament is due to direct gonadal effects and how much to prolonged instinctual frustration is not clearly known

Only a beginning has as yet been made in *therapeutic* studies of the personality deviations due to hypogonadism, but a variety of interesting problems are open to practical investigation with the use of the newer sex hormone products The problems are complex and other than hormone factors play large roles Many women report no conscious influence on the sex

drives following the use of hormone preparations, but occasionally uncomfortable erotization is experienced It is probably significant in this connection that sex impulses tend to be rather more generalized in women than in men and, as Benedek and Rubenstein have shown, the hormone factors bring about subtle changes of inner orientation of which the subjects may not be explicitly aware In the case of males, as Thompson and others have shown, the personality of the true hypogonad can be materially influenced by sex hormone administration Lacking this primary condition, however, such material seems to have little influence The use of gonad hormones in the treatment of homosexuality has had little success

Except in its grosser features, the relation of the *thyroid* to personality is not clear Complete deprivation of the thyroid hormone leads to imbecility Severe grades of the deficit characteristically give rise to bodily and mental sluggishness which gives the superficial impression of placidity Underlying this, however, can often be detected an attitude of sullen truculence In lesser grades of thyroid deficiency lack of ability for sustained endurance seems to be the outstanding characteristic It is perhaps the repeated frustrations thereby engendered which lead to dissatisfaction with life and to a variety of "neurotic" manifestations Psychological studies of hypothyroid patients receiving thyroid medication have not brought out any particularly illuminating data, though the subject has not been exhaustively studied Whether the alert aggressive type of human being owes his characteristics to more than usually generous supplies of thyroid hormone, as has often been claimed, is actually not known

As to direct relationships of *pituitary* hormones to personality, we are likewise but poorly informed Indirectly, the gland no doubt exerts an important influence by virtue of its relationship with the gonads A high incidence of pituitary disorders in "problem children" has been claimed by Mateer and others Rowe's and Lurie's evidence on this point was considered in a previous chapter A chief factor in the existing uncertainty is

the difficulty in making clean-cut diagnoses of lesser grades of pituitary disorder

Whatever be the uncertainties regarding primary influences, there is no question that the pituitary can give rise indirectly to profound modifications of the personality structure through its influences upon bodily *configuration* The man of diminutive stature is under a constant temptation to aggressiveness and pomposity as compensations for his littleness The gorillalike acromegalic or the bearded lady of the circus is never free of a demoralizing sense of disfigurement The giant, too, must live awkwardly in a world designed for those of lesser stature He often needs must stoop where others stand erect and cannot walk the streets without consciousness that the eyes of all are upon him The obese person lives under the constant necessity of exercising forbearance and fortitude to prevent serious warping of his personality As Mayers says, "He looks askance at chairs, he abhors public conveyances and the to him diminutive seats in halls and theaters He blocks aisles and passageways Would be humorous remarks fall upon his ears which grow continuously more sensitive despite valiant efforts to cultivate indifference He receives neither assistance nor sympathy The regular route of the seriously obese," Mayers concludes, "is through grief, sensitiveness and despair to isolation"

A genuinely satisfying discussion of the relationships of the endocrine glands to personality cannot yet be written Two essentials for inner health are a sound mind and a sound body Neither of these can be had without a considerable degree of endocrine normality Physical normality contributes importantly to wholesomeness of mental attitude and emotional balance Some things we know regarding the direct influence of the hormones upon the personality By and large, however, the problem remains mostly for future solution Even in broad outline, the picture is somewhat indeterminate and, in detail, is definitely confused The topic is perhaps the most important in the whole field of endocrinology Unfortunately, however, the psychological has been the most neglected aspect of the

subject Generally speaking, experimental endocrinologists are still in the organ preoccupation stage of scientific evolution in which the man who has the hormones enters little into their scheme of thinking Conversely, competent investigators in the field of psychology have been little attracted to the endocrine problems One of the outstanding needs in the field of endocrinology is better rapprochement between these two groups of workers

XV. ENDOCRINOLOGY OF THE FUTURE

THE ENDOCRINOLOGY of the past has been largely opportunistic and that of the present is scarcely less so Individual investigators have largely followed their own bent or exploited favorable situations as they have arisen The field has never been systematically cultivated as a whole and with adequate strategy planned in advance A few of the unsolved problems may be briefly discussed

The classical first experimental approach to the problem of hormone function is to remove a given gland and note the effects, either anatomical or functional, thus set up The next general step is to undertake to normalize the disturbed functions by administration of gland products The third logical step is to isolate the "active principle" of the given product and identify it chemically The final stage in an ideal schema is to reproduce the active agent by chemical synthesis The knowledge thus acquired can then be brought to bear on the alleviation of human ills Practically, however, no such logical development of the field has occurred The steps have often been taken in almost haphazard sequence Some of our most important endocrine knowledge has grown directly out of experiences with cases of glandular disorder—experiences that have sometimes long antedated scientific elucidation Many of the individual problems suggested by the schema remain for solution

Broadly speaking, the complete gamut of effects of *destruction* of any endocrine gland has never been adequately determined For example, it is quite unknown what effect parathy

roid deficiency may have upon the amount and composition of the bile Many similar gaps in knowledge could be mentioned Research in the future will no doubt continue to be addressed, in part, to the filling of such gaps The knowledge is especially needed by clinicians to aid them in reaching accurate diagnosis of endocrine defects in their patients

Similarly defective is our knowledge of the results of the *administration* of the various hormones What effect has androgen upon the motor functions of the digestive system? What is the influence of parathyroid hormone upon the development of the brain? Many such questions could be asked and each constitutes a problem for research Not only are the answers needed for the systematic rounding out of endocrine physiology and pathology, but likewise for the guidance of clinicians in their use of such substances in the treatment of disease It is important to know not only what are the immediate and intended effects, but also the by-effects, either good or bad In so far as knowledge is lacking, the physician must proceed blindly and may either do unwitting harm or fail to realize potential gain In short, we still need accurate determinations of many of the effects of each hormone on the functions of each of the organ systems—including such processes as weight, growth, development, irritability, motor and secretory activities, absorption, assimilation, and tissue metabolism

The necessity of determining the *chemical composition* of several hormones remains, as does also the succeeding problem of *synthesizing* as many of the active principles as possible No doubt, other important discoveries are still to be made of synthetic *substitutes* for the true hormones

As indicated earlier, there is much to be discovered regarding the *factors which influence the action* of hormones In the endocrine equation the tissue "y's" are quite as important as the hormone "x's" Riddle has found, for instance, that even so fundamental a reaction as the basal metabolic response to thyroid hormone may be largely influenced by the temperature

at which the test is made In the case of adrenin the blood pressure rises or falls, depending upon the amount that is injected. Similarly, the thyroid hormone may cause a marked gain or marked loss of weight, again depending upon dosage Responses in such cases are *diphasic* It would be desirable to know to what extent and under what conditions other hormones may give such contradictory results In addition to dosage—to reiterate—some other factors that are known, or are supposed to be important, are the degree of alkalinity of the tissues, the body temperature or that of the environment, diet, vitamin levels, and salt balance, and the levels of other hormones in the circulation. The influences of these and other variables are largely in need of systematic exploration.

A special phase of the problem of tissue reactivity is that of *acquired tolerance* In cases of some of the hormones, the more that is given the more must be given to produce the desired effect To what extent does the formation of antihormones account for the increased tolerance? To what extent is it a matter of establishing new glandular equilibria? Is it ever due to exhaustion of special reactive substances within the tissues? These are some of the possibilities that need further investigation

Another important variable in the operation of endocrine factors, and one that has received inadequate attention, is the *genetic*. It is known that the guinea pig is more reactive to some hormones than is the rat, and that the monkey may respond differently than the mouse. But our knowledge of *species differences* is only fragmentary. Not only between species, but even between strains within a given species, such variability is known to exist Riddle, for instance, has shown that twenty times as much prolactin is required to elicit a given crop response in one strain of doves as is needed to bring out the same reaction in another strain Some strains of rats are more susceptible to adrenal deficiency than are others. The topic is of special interest in relation to the human species. It is obvious that if one kind of person and his relatives were ten times as reactive to a given hormone as were members of some

other group, considerable differences in their liability to endocrine disorders might be thus set up One individual, for example, might succumb to exophthalmic goiter as a result of a given environmental strain and the other be left unscathed

A related problem is the extent to which the ability to produce hormones may be a matter of *heredity* As Stockard has emphasized in case of dogs, "endocrine types" are hereditary Thus, the Great Dane is a giant and the Pekingese a dwarf in the technical as well as the common sense of those terms The problem is twofold is the large dog a giant because of an hereditary high level of efficiency of his pituitary gland or because of high susceptibility to the growth hormone? Stockard's data rather favor the second possibility

From the standpoint of practical medicine, the most important aspect of heredity is that relating to endocrine diseases, as such From this point of view it is more or less immaterial whether the thing that is inherited is a special susceptibility to a given hormone or a special level of glandular efficiency If one's grandmother dies of exophthalmic goiter, is there any special likelihood of his developing the same disease? Or is there such a thing as a hereditary tendency to endocrinopathy in general? In other words, would exophthalmic goiter in a parent indicate any particular liability to Addison's disease in his offspring? Other obvious questions in genetics are whether endocrine peculiarities may be sex linked—as seems to be the tendency to hemophilia—whether the factor is dominant or recessive, and whether the endocrinopathy is singly or multiply determined These ramifications of the general problem would give scope for many investigators working many years

More knowledge is needed of the operation of endocrine factors in the different *epochs of life* Relatively little is known regarding the influence of hormones on the organism *before birth* The developing baby obtains its sustenance from the blood stream of the mother The placenta is permeable to hormones as it is to all of the various substances that go to make up the growing body The endocrine conditions in the mother

as well as in himself, therefore, undoubtedly influence the development of the child One characteristic happening in pregnancy is hypertrophy of the anterior lobe of the maternal pituitary This may be an adaptive reaction whereby the growth of the fetus is promoted The mother herself is also subjected to the excessive output of growth hormone, as is indicated by the occasional occurrence of acromegalic changes and especially coarsening of the features in pregnant women The secretion of "witch's milk" by newborn infants seems to be another manifestation of response to endocrine changes in the mother In 1910, Hoskins reported an investigation having as its purpose an attempt to influence fetal development by the administration of a hormone—in this case thyroid—to the mother Occasional reports have since appeared of studies of other single aspects of the problem, but it is in need of systematic investigation as a whole

The hormone status of the mother is probably reflected also in the process of lactation Careful study is needed of the possibility that development in the early *infantile* months is in a measure controlled by the endocrine system of the mother Not only should the quality of the mother's milk as a nutrient substance be further investigated in relation to her endocrine functions but the actual hormone content of the milk would bear investigation Possibly some of the obscure metabolic disorders of infants could thus be explained It is not improbable that some of the difficulties arising in the artificial feeding of babies may be due to differences arising in the hormone content of mother's milk as compared with that of other animals that may be employed

There are many gaps in our knowledge of the endocrine physiology in the *prepuberal* years This comes about no doubt in considerable measure from the fact that kittens and puppies are not very satisfactory as experimental animals, hence the fundamental studies upon which endocrine advancement largely depends have been made mostly upon adult animals *Enough is known strongly to suggest that the younger sub-*

jects are importantly different from the older in their endocrine status, but details are mostly lacking This gap is especially unfortunate because during the prepuberal years the individual in numerous respects is marked for life To the pediatrician, endocrinology is of very special importance But in large measure he has been left without the necessary fundamental information upon which to develop the clinical aspects of the subject

Of recent years the period of *puberty* has received a good deal of study because of the fact that the characteristic changes of this epoch afford especially instructive data in regard to the action of thyroid, pituitary, and gonad hormones After the hazards of puberty have been met, the endocrine situation, except as disease may intervene, remains fairly constant throughout the *adult* period to the onset of the *climacteric* It is during this epoch that present-day knowledge of endocrine physiology is most nearly adequate

The endocrinology of the *senile period*—and especially our ignorance of it—was discussed in the preceding chapter The fact that this period is becoming increasingly a matter of social and scientific concern offers hope that future studies on the pertinent endocrinology may be more numerous and more fruitful To what extent is senescence determined by hormone factors What could be done by control of these, either to delay its approach or to mitigate its effects? It would be unfortunate to see in this problem nothing but that of sexual rejuvenation From the broadly biological point of view, the individual who has made his contribution to the perpetuation of the species is a superfluity, but from the more narrowly human point of view, the mere passing of years is not in itself an adequate reason for euthenasia. The old man, if with age he has attained wisdom, still has social value In any case, as a matter of fact, the older group will be with us in greater numbers in the future than in the past, and hence demands more attention The mere prolongation of existence may be a dubious boon, but anything that would add to the productivity and the enjoyableness of the last

years would be desirable In any case, as a matter of rounding out knowledge, the endocrinology of senescence and senility is in need of further systematic investigation As in various other instances, this general problem breaks down particularly into two subproblems, namely, the reactivity of the senile tissues to the various hormones and relative efficiency of hormone production by the individual's own glands

A problem that is ever with us, and toward the solution of which progress is but slow, is that of the *control of the endocrine glands* The hormones largely regulate the body but what regulates the regulators? We know that excitation of the sympathetic nervous system by emotions or otherwise causes a discharge of adrenin The thyroid gland seems to share in the excitation Erotic excitement seems to stimulate the pituitary—which fact may afford at least a part of the biological rationale for courtship Some glands are set into activity by the hormones of other glands and some, perhaps, are depressed by similar agencies Most significantly, we know that the glands of most people most of the time are by one agency or another kept in a suitable state of activity or of quiescence By and large, how ever, our knowledge of the control of hormone secretion is in a fragmentary state As a particular phase of this problem, the question of *secretory centers* in the brain needs investigation There is reason to believe that to this end it would be profitable further to explore the hypothalamic region Especially do we need to know the effects of prolonged *emotional strain* and of *environmental vicissitudes* on the various glands When psy chologists come seriously to grips with the aspects of endocrinol ogy in which they are especially concerned, they will insist upon much more adequate knowledge than is as yet available regarding the repercussions of life experiences in the endocrine apparatus Many individual problems—and they promise mostly to be difficult problems—will have to be solved before we can walk with assurance in this part of our field

In an earlier paragraph, stress was laid on the desirability of determining the influence of the various hormones in each

of the organ systems Special importance attaches, however, to the *nervous system* It is known that thyroid deficiency in tad poles results in marked lagging of brain development and that the offspring of human mothers suffering from serious thyroid deficiency often show a comparable condition During infancy and afterwards, thyroid deficiency can likewise bring about all degrees of mental retardation But when these facts have been recited, we are about at the end of the story as it is known to day The mere statement of this fact implies the need for many studies of hormone factors in brain development and func tion It is probable that different parts of the brain should be investigated separately There are suggestions that the ancient thalamic region where the vegetative processes are controlled shows special relationships to the hormones It is here, perhaps, that the internal secretions chiefly impinge in exerting their important influences upon the instinctual life

From the standpoint of the clinician, with his interest in symptomatology, the relationship of the hormones to the func tioning of the *autonomic nervous system* is a matter of special importance To some extent, the influence of endocrine factors upon the sympathetic system has been systematically investi gated, but less attention has been paid to the parasympathetic system Many large and important problems on the influence of known hormones and of glandular defects throughout the nervous system are open to investigation

In addition to studies of the type suggested—at the various segmental levels—the relation of the hormones to nervous activity should be investigated also in terms of *behavior* Just enough is known in this part of the field to indicate clearly the need for knowing much more By the use of an estrogen prep aration, Bard has been able to induce in a spayed cat a state of prolonged estrus in which the complex reaction pattern with its curiously ecstatic episodes was maintained for weeks on end The influence of prolactin on the maternal behavior pattern as described in a previous chapter is another case in point Allee's experiments on individual dominance in flock hierarchies of

chickens as influenced by administered hormones affords another illuminating approach to the general problem Such permeative changes in behavior through the influence of hormone agents may be designated, as previously suggested, by the term *chemical conditioning* The part played by such conditioning in determining behavior patterns, generally, is in need of more searching study One special phase of the problem is the maturation of the instinctual drives Courtship, nesting, and a variety of other modifications of behavior can perhaps best be elucidated in such terms

The question has been raised to what extent conditioning in the ordinary sense may depend upon hormone factors and to what extent experimental conditioning and hormonal conditioning may amount fundamentally to the same thing That a genuine relationship exists is indicated by the work of Hartman and Liddell These investigators, by a process of experimental conditioning, first set up in sheep a condition that is strongly suggestive of psychoneurosis in man The "neurotic" symptoms were largely ameliorated by adrenal-cortex extract —to reappear when the treatment was discontinued Hartman's studies indicate that cortin is in itself harmless How useful would it be to tide human beings over times of special stress or to give relief from neuroses after they have become established? Would some sort of neuroses be influenced and others not? The whole problem of hormone factors in neurotic behavior needs further study

As indicated in a previous chapter, more knowledge is needed of the influence of the hormones in *non endocrine diseases* generally It is a well known fact that persons having diabetes are prone to boils and to cataract There is some evidence that susceptibility to poliomyelitis may be determined by hormonal influences Antibody formation and other immunity mechanisms are to some extent known to be modified by these same factors Claims have been made that arthritis may be influenced in its incidence or in its course by hormones Adrenal deficiency increases the vulnerability to the toxins of

bacteria and the same is probably true of those engendered by metabolic disturbances Other hints of this sort could be cited but they would not go far to mitigate our vast ignorance One of the major needs, then, is an adequate determination of the influences of the hormones on the incidence and progress of diseases in general Endocrinology will not have reached its full fruition in practical medicine until such relationships shall have been clearly worked out To this end we especially need a more adequate quantitative pathology of the endocrine glands and better means of appraising the hormone titers in the circulating blood

It is a substantial sign of progress that practical physicians are becoming more increasingly alert to the importance of *psychological medicine* But endocrinologists have as yet shared by no means fully in the growing enlightenment Their thought is mostly still of thyroids, of estrus, of growth, or what not, but little attention is given by them to the individual as such Equally unfortunate is the hesitancy of trained investigators in the field of psychology to find a scope for their work in the field of the endocrine glands Thus, one of the major problems in the field, that of the relationship of the hormones to personality, continues largely to go by default

We are told of the subdued truculence of the hypothyroid and of the stridulant captiousness of the hypogonad subject We are assured, but without arousing much conviction, that problem children are often victims of glandular perturbations There are claims that irascibility can be corrected by parathyroid extract Hyperinsulinism has, as a matter of record, led to diagnoses of hysteria and of dementia praecox Thyroid deficiency, according to Bleuler, sometimes leads to a psychosis that cannot be differentiated clinically from schizophrenia and hyperthyroidism can lead to acute mania Cases are on record of women who have become so uncomfortably erotized by taking estrogen as to refuse to go on with the treatment. Sweeping claims have been made of the value of sex hormones in the treatment of involutional melancholia—but many failures also

are recorded Many psychiatrists suspect that endocrine factors may be of importance in other mental disorders, but how valid is the suspicion remains largely to be determined Perhaps no other aspect of endocrinology is so meaningful in terms of ultimate human welfare as that of its relationship to personality and its disorders

Medical and biological investigation has as its ultimate goal the improvement of health and happiness Of the various aspects of biology, the study of the hormones is particularly attractive because of the applicability of its advances It must be recognized, however, that application now lags well behind research in many parts of the field Endocrinology is a broad subject Hormone influences permeate the life processes in all their known aspects The science, however, is still in an early phase of its evolution There are now apparent many problems, the solution of which is obviously important As expansion continues, many more will inevitably emerge Endocrinology has already contributed much to human welfare The promise of other far reaching contributions is bright

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Index Catalog of the Surgeon General's Library This, supplemented by the files of the Quarterly Cumulative Index Medicus, affords a practically complete bibliography of endocrinology

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